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THE EFFECTIVENESS OF A COMMUNITY-  
BASED EXERCISE AND EDUCATIONAL  
PROGRAMME ON DEPRESSION IN GREEK  
POPULATION WITH PARKINSON'S DISEASE

T CHATZIDAMIANOS

PhD                      2018

# THE EFFECTIVENESS OF A COMMUNITY- BASED EXERCISE AND EDUCATIONAL PROGRAMME ON DEPRESSION IN GREEK POPULATION WITH PARKINSON'S DISEASE

THEODOROS CHATZIDAMIANOS

A thesis submitted in partial fulfilment of the  
requirements of Manchester Metropolitan  
University for the degree of Doctor of  
Philosophy

Department of Health Professions  
Manchester Metropolitan University

2018

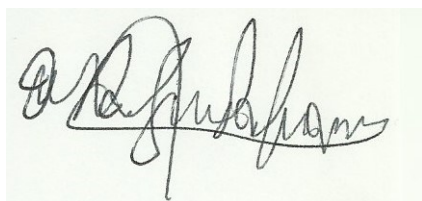
## **AUTHOR'S DECLARATION**

I declare that this work is original, the result of my own work and no material within the current thesis has been previously submitted in support of an academic award, course or qualification at Manchester Metropolitan University or any other institution of learning. Furthermore, I declare the current thesis complies with the Institutional Code of Practice for Postgraduate Research Degrees.

Date: 18<sup>th</sup> June 2018

Name: Theodoros Chatzidamianos

Signature:

A handwritten signature in black ink on a light green background. The signature is cursive and appears to read 'Theodoros Chatzidamianos'.

## ACKNOWLEDGEMENTS

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This research would not have been possible without the subjects, who volunteered in the present survey and RCT; and they taught me about Parkinson's disease, and be grateful for being healthy and can make dreams for my life.

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Theodoros

## DEDICATION

This thesis is dedicated to my family

Smaller (Parkinson)  
My world got smaller  
My handwriting got smaller  
My voice got smaller  
My walk got smaller  
My spirit got smaller  
My balance got smaller  
It crept upon me in micro  
increments.  
The space and the world got  
smaller  
And then it became big and  
scary and then it had a name.  
These are big words for small  
and slow until it arrived  
with a name: PARKY

Written by one participant of the RCT

## **ABSTRACT**

Depression is among the most common symptoms of Parkinson's disease (PD); and its estimated prevalence is 35%. A systematic review revealed that there is insufficient evidence to draw strong conclusions about the antidepressant effects of exercise in PD. Hence, in order to address this important question, a randomised controlled trial (RCT) was conducted in Greece.

To aid the design of the RCT, a patient survey was performed which indicated that PD affects both physical function and mental health, even from the first stages of the disease; and the most prevalent responses were considered for the design of the RCT.

The RCT, examined whether a community-based exercise and educational programme could produce short- and longer-term antidepressant effects in depressed patients with PD. Eligible participants were allocated either to a supervised group-based exercise and educational programme (intervention group) or an unsupervised individualised home-based training (comparison group). The findings revealed no significant differences between the two groups at the end of the treatment and three-month follow-up period. However, one-way repeated measures of ANOVA showed that the depressive scores were significantly improved in the intervention group over time ( $p = .00$ ;  $t_1-t_2$ :  $p = .00$ ;  $t_1-t_3$ :  $p = .01$ ), and the magnitude of the effect was medium ( $t_1-t_2$ :  $r = .40$ ;  $t_1-t_3$ :  $r = .31$ ). Improvements in mood were also reported by the participants. The intervention also had positive effects on anxiety levels, motor function and quality of life.

The findings of this thesis showed that the treatment potential is high; and a simple community-based exercise and educational programme, without the use of expensive and sophisticated equipment, can be prescribed for depression in patients with PD.



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## LIST OF ABBREVIATIONS AND ACRONYMS

1-RM:	1-repetition maximum
2MWD:	2 -minute walking distance
2MWT:	2-Minute Walk Test
5-HT:	serotonin
6MWT:	6-Minute Walk Test
ABCS:	Activities-specific Balance Confidence Scale
Ach:	acetylcholine
ACTH:	adrenocorticotrophic hormone
ADL:	activity of daily living
AF:	attendance form
AHA:	American Heart Association
ANOVA:	One-way Analysis of Variance
ATS:	American Thoracic Society
BAI:	Beck Anxiety Inventory
BBS:	Berg Balance Scale
BDI:	Beck Depression Inventory
BDNF:	brain-derived neurotrophic factor
BG:	basal ganglia
BLT:	bright light therapy
BMI:	body mass index
CANMAT:	Canadian Network for Mood and Anxiety Treatments
CBT:	cognitive-behavioural treatment
CG:	comparison group
CMS:	cognitive movement strategies
COMT:	catechol-O-methyltransferase
CONSORT:	Consolidated Standards Of Reporting Trials
COPD:	chronic obstructive pulmonary disease

CROMs	clinician-reported outcome measures
DA:	dopamine
DBP:	diastolic blood pressure
DBS:	deep brain stimulation
DSM:	Diagnostic and Statistical Manual of Mental Disorders
DST:	dexamethasone suppression test
ECG:	electrocardiogram
ECT:	electroconvulsive therapy
ELISA:	enzyme-linked immunosorbent assay
EMT:	expiratory muscle training
EPDA:	European Parkinson's disease Association
FD:	falls diary
FES:	Tinetti Falls Efficacy Scale
FES-I:	Falls Efficacy Scale International
FEV <sub>1</sub> :	forced expiratory volume in the first second
FOF:	fear of falling
FOG:	freezing of gait
FQ:	falls questionnaire
FRC:	functional residual capacity
FVC:	forced vital capacity
GAD:	general anxiety disorder
GDNF:	glial-derived neurotrophic factor
GDS:	Geriatric Depression Scale
GHQ:	general health questionnaire
H&Y:	Hoehn and Yahr
Ha:	experimental (alternative) hypothesis
HADS:	Hospital Anxiety and Depression Rating Scale
HADS-A:	Hospital Anxiety and Depression Scale- Anxiety
HADS-D:	Hospital Anxiety and Depression Rating Scale- Depression
HAM-D:	Hamilton Depression Scale

Ho:	null hypothesis
HPA:	hypothalamic–pituitary–adrenal
HPDA:	Hellenic Parkinson’s disease Association
HR:	heart rate
HR <sub>max</sub> :	maximum heart rate
HRR:	heart rate reserve
ICD:	International Statistical Classification of Diseases
IG:	intervention group
IL-6:	Interleukin 6
IMT:	inspiratory muscle training
IVC:	inspiratory vital capacity
KAPI:	Elderly Open Care Centres
L-dopa:	levodopa
LPDQ:	Levine-Pilowsky Depression Questionnaire
M-PAS:	Modified Parkinson Activity Scale
MADRS:	Montgomery-Asperg Depression Rating Scale
MAO-B:	monoamine oxidase B
MAOIs:	monoamine oxidase inhibitors
MCID:	minimal clinically important difference
MDD:	major depressive disorder
MDE:	major depressive episode
MDS:	Movement Disorder Society
METS:	Metabolic Equivalent of Task
Mini-BESTest:	Mini-Balance Evaluation Systems Test
MIP:	maximal inspiratory pressure
MMSE:	Mini-Mental State Examination
MoCA:	Montreal Cognitive Assessment
MRI:	magnetic resonance imaging
MS:	multiple sclerosis
NA:	noradrenaline

NHS:	National Health System
NICE:	National Institute for Clinical Excellence
NPF:	National Parkinson Foundation
PD:	Parkinson's disease
PDD:	persistent depressive disorder
PDQ-8:	Parkinson's Disease Questionnaire 8
PDQ-39:	Parkinson's Disease Questionnaire 39
PDQL:	Parkinson's Disease Quality of Life Questionnaire
PEDGE:	Parkinson Evidence Database to Guide Effectiveness
PEDro:	Physiotherapy Evidence Database
PHQ-9:	Patient Health Questionnaire 9
PICOS:	population, intervention, comparison, outcome and study design
PE <sub>max</sub> :	maximal expiratory mouth pressure
PI <sub>max</sub> :	maximal inspiratory mouth pressure
PIMS:	Parkinson's Impact Scale
PRISMA:	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PROMs:	patient-reported outcome measures
QoL:	quality of life
RCT:	randomised controlled trial
ROM:	range of movement
RV:	residual volume
SAD:	social anxiety disorder
SAFFE:	Survey of Activities and Fear of Falling in the Elderly
SBP:	systolic blood pressure
SCOPA-S:	Scales for Outcomes in PD-Sleep Scale
SCOPA-PS:	Scales for Outcomes in Parkinson's Disease–Psychosocial
SD:	standard deviation
SDS:	Zung-Self Rating Depression Scale
SEADL:	Schwab and England Activities of Daily Living
SEE:	Self-Efficacy for Exercise

SI:	summary index
SN:	substantia nigra
SNRIs:	serotonin–norepinephrine reuptake inhibitors
SOP:	standard operating procedure
SpO <sub>2</sub> :	oxygen saturation (measured by pulse oxymetre)
SPSS:	Statistical Package for the Social Sciences
SQ:	Satisfaction Questionnaire
SSRIs:	selective serotonin reuptake inhibitors
STAI:	State-Trait Anxiety Inventory
TCAs:	tricyclic antidepressants
TLC:	total lung capacity
TUG:	Timed Up and Go
UK:	United Kingdom
UK PDS:	United Kingdom Parkinson' disease Society
UNT:	urinary neurotransmitter testing
UPDRS:	Unified Parkinson's Disease Rating Scale
URL:	uniform resource locator
VEGF:	vascular endothelial growth factor
WHO:	World Health Organisation

## GLOSSARY

**Aerobic exercise:** movement or activity which primarily utilises the body's oxygen energy system (Whipp et al., 1981).

**Anaerobic exercise:** movement or activity which primarily utilises the body's anaerobic system- hydrolysis of creatine phosphate or anaerobic glycolysis (Kleisouras, 1997).

**Exercise frequency:** the number of sessions delivered per week (Shanahan et al., 2015).

**Group exercise:** two or more participants in an exercise session (Perraton et al., 2010).

**Individual exercise:** exercise performed in a separate area to the other participants in the trial and separate from other people who are exercising (Perraton et al., 2010).

**Mode of exercise:** the specific sport or activity used (Perraton et al., 2010).

**Multi-modal training:** exercise programme that incorporates several types of exercise (e.g. resistance, stretch, aerobic) to improve multiple aspects of fitness (e.g. muscle strength, endurance, flexibility, aerobic capacity) (Kleisouras, 1997).

**Off-state:** the time period the antiparkinsonian medication stops working and the cardinal motor symptoms of PD appear (Shulman, 2010).

**On-state:** the time period the antiparkinsonian medication is effective and the PD motor symptoms are limited (Shulman, 2010).

**Session duration:** the length of each session during the rehabilitation programme.

**Supervised exercise:** any exercise monitored or watched by one or more persons as a part of the trial (Perraton et al., 2010).

**Wearing off:** The gradual return of symptoms that occurs at the end of a dose of levodopa. This pattern appears when a person with Parkinson's disease has been using levodopa for many years (Shulman, 2010).

**«Η ολοκλήρωση της διδακτορικής διατριβής συγχρηματοδοτήθηκε μέσω του Έργου «Υποτροφίες ΙΚΥ» από πόρους του ΕΠ «Εκπαίδευση και Δια Βίου Μάθηση», του Ευρωπαϊκού Κοινωνικού Ταμείου (ΕΚΤ), ΕΣΠΑ, 2007-2013».**

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# **CHAPTER 1**

## **INTRODUCTION TO STUDY**

### **1.1. Statement of the problem**

Idiopathic or primary Parkinson's disease (PD) is a progressive, neurodegenerative, movement disorder of the extrapyramidal system; whose aetiology is unknown (Jankovic, 2008). PD affects all the nations and countries; and the estimated total population of individuals affected by PD worldwide is 7.5 million. The prevalence of the disease is relevant high in population over the age of 65; and the number of sufferers is expected to increase the following decades in Western countries, due to the aging of the population (Pringsheim et al., 2014). The disease is characterised by motor and non-motor features, with depression being the most common mental disorder, affecting about 35% of PD population (Goldman and Postuma, 2014). It is well established that PD affects negatively the sufferers and their carers, leading to disability and caregivers' burden; and increases healthcare utilisation. Depression may affect further the impacts of the disease, and it is indicator for poor disease prognosis (Lépine and Briley, 2011).

The focus of research has primarily been on the motor symptoms of PD; whereas the non-motor symptoms, such as depression, have been less studied. Current treatment for depression in PD includes mainly pharmacological treatment and psychotherapy. However, there is limited evidence about their effectiveness, and the findings of experimental studies are mixed (Chen and Marsh, 2013). Therapeutic exercise may be an important adjunct to the available pharmacological and psychological treatment for the management of depression in PD. However, a limited number of experimental studies were found to assess the effects of therapeutic exercise on depressive levels in PD population as primary outcome measure.

To our knowledge, there is little research about PD in Greece; a European country where the percentage of senior population has gradually increased; and the prevalence of age-related disorders, such as PD, is expected to be higher in the future. In addition, there is need for low-cost treatment approaches, as due to the ongoing debt crisis the Greek government and the citizens face difficulties in covering all the health expenditures.

## **1.2. Aims of the thesis**

Based on the gap in the literature, the current study was conducted, whose aims are listed as follows:

1. To evaluate the effects of physical activity on anxiety and depression in patients with PD.
2. To detect and list the impacts of PD on everyday activities and emotional status in patients with PD living in Greece.
3. To design and evaluate a group-based exercise and educational programme to improve depression, mobility, quality of life (QoL) and lung function in Greek PD population suffering from depression.

A systematic review was conducted to satisfy the first aim of the thesis, a survey the second, and a randomised controlled trial (RCT) the third. The gap in the literature that arose from the systematic review, indicated the need for a well-designed experimental study to assess the effectiveness of a community-based programme to relieve depression in a PD population. The survey gave direction as to what was important from patients' perspective. The results of these two studies then informed the design of the RCT.

## **1.3. Elements of originality and contribution to knowledge**

The current study was held in Athens, Greece. The overall investigation was under the supervision of Manchester Metropolitan University in collaboration with the Hellenic Parkinson's disease Association (HPDA) 'Επικouρος-kinisi' (Επίκουρος- κίνηση), as this organisation seems to have the largest database of Greek PD patients. The study was funded by the States Scholarship Foundation (Ίδρυμα Κρατικών Υποτροφιών) of Greece. To our knowledge at the time of conduction of the present study, there were no other similar studies undertaken or proposed to be undertaken on PD population in Greece. In addition, no previous systematic review was founded to evaluate solely the effects of physical activity on anxiety and depression in patients with PD. As the research should be linked with the clinical practice; the findings of this study would be useful to assist physiotherapists working in Greece, to take clinical decisions based on the needs of PD

patients, and promote the community-based therapeutic exercise in Greeks patients affected by PD.

#### 1.4. Dissertation guidance

The dissertation is divided into 11 Chapters. Chapters 2-4 provide the rationale behind the conduction of the RCT; Chapters 5-7 are referred to the survey, and Chapters 8-10 to the RCT. Chapter 11 is the final conclusion of the thesis. The title and content of each Chapter are summarised in table 1.1.

**Table 1.1.** Chapters of the thesis.

Chapter	Title	Content
2	Landscape of Greece	Brief description of the country, where the present study was conducted
3	Background of study	Literature review on PD and depression in PD
4	Systematic review	Evaluation of the effects of therapeutic exercise on anxiety and depression in PD population
5	Survey-methodology	Design of the survey
6	Survey-results	Survey's findings
7	Survey-discussion	Interpretation of survey's findings
8	RCT-methodology	Design of the RCT
9	RCT-results	RCT's findings
10	RCT-discussion	Interpretation of RCT's findings
11	Overall conclusion	Final conclusions and future directions

Acronyms. PD: Parkinson's disease; RCT: randomised controlled trial.

# **CHAPTER 2**

## **LANDSCAPE OF GREECE**

### **2.1. Introduction**

As the current study was held in Athens, Greece, this chapter provides a brief description of the landscape of Greece. It contains a geographical and demographic description, the current status of the country, basic information about the healthcare system and PD in Greece; indicating the rationale for conducting the present study in this country.

### **2.2. Geography of Greece**

Greece is a Mediterranean country of Southern Europe on the southern tip of the Balkan Peninsula; located at the crossroads of Europe, Asia and Africa. The official name of the country is Hellenic Republic; however, in the current thesis the name Greece was preferred, as it is known worldwide. Greece covers 131,944 square kilometers of land; 20.2% of them being islands. Greece is the second more mountainous country of Europe; and mountains cover 80% of the country. About 30% of Greece is forested. The climate of the country is mainly Mediterranean; but due to its landscape, it varies from Mediterranean to Alpine. The capital of the country is Athens, located in the southern part of the mainland. The geomorphology of the city varies, as it extends from the coastline to the mountains, including flat plain zones and hills. The official language is Greek, including several dialects; but all the citizens speak demotic Greek (δημοτική γλώσσα), a form of Modern Greek. The Greek language has its own writing system, which shares elements with the Latin and Slavic alphabet (Encyclopaedia Ydria, 2014).

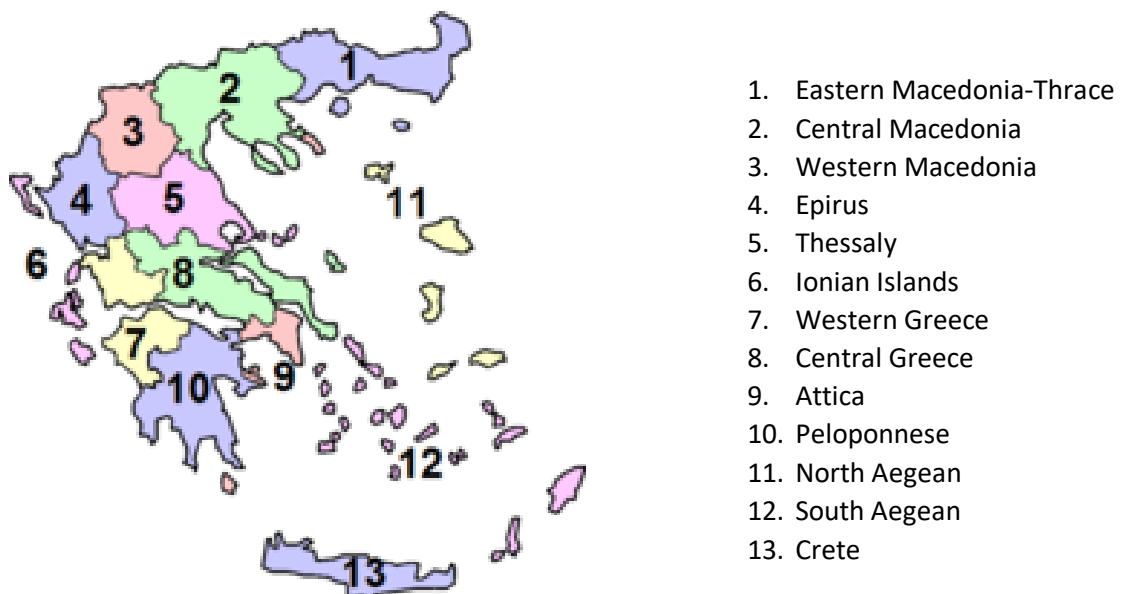
### **2.3. Demographic profile**

The total population of Greece was estimated at 11.5 million people on 1<sup>st</sup> January 2018. However, the real population may be higher, as it is believed that the number of undocumented immigrants is between 0.4 and 0.5 million. Over 45% of the country's population lives in the two main cities: Athens (4.5 millions) and Thessaloniki (1.1 million). The vast majority of Greek citizens are Greek. However, there is a Muslim minority in Thrace (~ 100,000) and approximately 170,000 Roma. The percentage of foreign population is estimated around 8.3% to the total population; whereas 70% of them are from other

Balkan and ex-Soviet Union countries, mainly from Albania. Life expectancy is 80.3 years, among the highest in the world. The phenomenon of the aging of Europe is obvious in Greece. Greece's population census of 2011 revealed that 19.3% of the total population was above the age of 65 (Encyclopaedia Ydria, 2014). As the total number of the senior population is projected to increase greatly the following decades, the prevalence of age-related disorders (such as PD) is also expected to be higher.

#### 2.4. Administrative divisions

The country is divided in 13 administrative units (Περιφέρειες) (image 2.1), 51 regional units (Νομοί) and the Eastern Orthodox monastic community on Mount Athos (image 2.2, p. 8), which is an autonomous self-governing entity. Athens Metropolitan Area occupies almost all Attica administrative and regional unit including four urban areas: Athens, Piraeus, West Attica and East Attica (Encyclopaedia Ydria, 2014). Both the paper-based survey and the RCT were conducted in Athens Metropolitan Area.



**Image 2.1.** Administrative units of Greece (adopted from Wikipedia).



1. Attica; 2. Euboea; 3. Evrytania;
4. Phocis; 5. Phtiotis; 6. Boeotia; 7. Chalkidiki; 8. Imathia; 9. Kilkis; 10. Pella; 11. Pieria; 12. Serres; 13. Thessaloniki; 14. Chania; 15. Heraklion; 16. Lasithi; 17. Rethymno; 18. Drama; 19. Evros; 20. Kavala; 21. Rhodope; 22. Xanthi; 23. Arta; 24. Ioannina; 25. Preveza; 26. Thesprotia; 27. Kerkyra; 28. Cephalonia; 29. Lefkada; 30. Zakynthos; 31. Chios; 32. Lesbos; 33. Samos; 34. Arcadia; 35. Argolis; 36. Corinthia; 37. Laconia; 38. Messenia; 39. Cyclades; 40. Dodecanese; 41. Karditsa; 42. Larissa; 43. Magnesia; 44. Trikala; 45. Achaia; 46. Aetoloacarnania; 47. Elis; 48. Florina; 49. Grevena; 50. Kastoria; 51. Kozani; a. Mount Athos.

**Image 2.2.** Regional units of Greece and Mount Athos (adopted from Wikipedia).

## 2.5. Modern history

In the 1900s the country experienced many wars and changes of the government, which hindered economic development, and were responsible for a high number of casualties and immigration of Greeks to other countries. The Greek Civil War (1946-1949) was the last war occurred in the country. After the end of the Greek military junta (1967-1974), the Hellenic Republic was established. Greece joined European Union in 1981. It became a member of Schengen Area in 2000 and adopted the euro currency in 2002. From 1970s to 2000s, the economic growth of the country was among in the highest in Europe. In 2000s the relative purchasing power of Greeks was almost equal to that of the rest Western European countries and the QoL was among the top 20 in the global ranking system (Encyclopaedia Ydria, 2014).



However, since 2009, Greece has been undergoing the most severe debt crisis in its history since the end of the Greek Civil War. In 2010, the Greek Government signed a financial rescue package with Troika; comprising by the European Commission, the European Central Bank and the International Monetary Fund. Capital controls were introduced in June 2015, and a referendum took place in July 2015 to decide whether Greece was to accept the bailout conditions proposed by Troika. The two last events were occurred during the conduction of the current RCT. Since 2015, the financial crisis has been further affected by the refugee crisis. The arrivals of refugees by sea from Turkey seeking asylum have increased, due to the ongoing Syrian War; and refugee camps have been established all over the country (Pelekanou, 2017).

The ongoing crisis had several impacts on the Greek population. In particular, unemployment rates reached 28% in 2013, the income of citizens was reduced by 40% from 2009 to 2014; 22.2% of the population were “severely materially deprived” in 2015, and depression rates were increased from 3% in 2008 to 9% in 2009. It is also estimated that 300,000 Greeks migrated to other countries from 2009 to 2015. In addition, the Greek National Health System (NHS) was badly damaged. Before crisis, the Greek NHS was ranked 14<sup>th</sup> worldwide in the overall assessment, above from other European countries, such as the United Kingdom (18<sup>th</sup> place). However, healthcare expenditure per capita was reduced by 28% from 2009 to 2011, and there is a shortage of staff and medical equipment in public hospitals and clinics. Thus, there are indications that the Greek NHS could potentially collapse (Pelekanou, 2017).

## **2.6. Health delivery system**

The health services in Greece are either public, provided by the Greek NHS, or private. However, some private organisations are enrolled with the Greek NHS, which covers a part of the patients’ expenditure in the private domain. Physiotherapy services for outpatients are provided by hospitals and clinics, physiotherapy centres or home-based physiotherapy services in patients’ home. With respect to senior citizens with disability, the majority live alone in their own houses or with their children. They receive mainly care by their family

or a caregiver, who is mainly a woman for Eastern Europe without any qualification. A small percentage lives in nursing homes, due to the stigma of not taking care of the elderly parents, and disdain of many people to this kind of care. However, a special public structure are Elderly Open Care Centres (KAPI), which are located in all the Greek municipalities. The main objective of KAPI is the elderly to stay physically and socially active. These structures are open in working days, from morning to evening; and provide a variety of services, usually free-of-charge; such as physiotherapy, social support, artistic activities and trips.

## **2.7. Parkinson's disease in Greece**

There is little research about PD in Greece, usually genetic studies. Even the exact number of PD sufferers is unknown (section 3.2). There are two non-profit organisations to promote health and welfare of people living with PD, their families and caregivers: the HPDA 'Epikouros-kinisi' and Northern Greece Parkinson's Disease Association. Both of them are members of the European Parkinson's Disease Association (EPDA). The HPDA was founded in 2007 and is based in Athens, whereas the Northern Greece Parkinson's Disease Association in 2016 in Thessaloniki. The HPDA organises annual symposiums in Athens to keep patients and their caregivers updated about the management of the disease. Group exercise classes were provided with a minimum cost at the 5<sup>th</sup> Annual Symposium in 2014, and a booklet with exercises in a seated position was delivered to the participants. The vast majority of patients were interested to participate in such programmes in the future.

Patients with PD living in Greece face many challenges. The majority of them live in their properties and receive care by their family. Due to the geomorphology of Greek cities and villages –characterised by downhills, uphill and stairs–, the patients reduce their outdoor activities, even from the first stages of the disease. Apart from the pharmacological treatment, the free-of-charge services provided by the Greek NHS in outpatient PD population is limited. Thus, the majority of patients have to pay by themselves the physiotherapy cost. Due to inability to cover the expenditures, they usually start physiotherapy at the middle stages of the disease; when the symptoms and the impacts of PD are more apparent. The physiotherapy programmes are almost individualised, as

community-based programmes are not popular in Greece. Patients living in small cities and rural areas should travel to Athens or Thessaloniki to visit specialist neurologists or PD centres, increasing further the indirect cost of the disease. Hence, there is need for low-cost physiotherapy programmes, such as group-based exercise, easily accessible to the vast majority of patients; in order to reduce the treatment cost, maintaining a high quality of service.

# **CHAPTER 3**

## **BACKGROUND OF STUDY**

### **3.1. Introduction**

The literature review provides the background and justification for research (Bruce, 1994). The current chapter is a synthesis of the literature about PD and comorbid depression; providing an in depth understanding of the prevalence, pathophysiology, symptoms, impacts and treatment options.

### **3.2. Epidemiology of Parkinson's disease**

PD is the most common movement disorder, and the second most common neurodegenerative disease after Alzheimer's disease (Elbaz et al., 2016). Life expectancy is between 6.9 to 14.3 years following diagnosis, or 11 years shorter to that of the overall population (Macleod et al., 2014). However, it is not clear whether the short life expectancy of PD sufferers is due to the disease itself or from accompanying motor and non-motor dysfunctions, such as falls and aspiration pneumonia (Macleod et al., 2014).

The disorder affects all the races and ethnic groups; but is somewhat more prevalent among Caucasians (100-350/100,000) (Elbaz et al., 2016); whereas less among Asian populations (35-176/100,000) (Muangpaisan et al., 2009), and black Africans (20-30/100,000) (Okubadejo et al., 2006). It is under debate if these differences are related to environmental and genetic factors, which are believed to be risk factors for the onset of the disease (section 3.3) (Elbaz et al., 2016); or reflect differences in the methodology of epidemiological studies. In addition, the low prevalence in Africa may be due to the local population structure, as life expectancy and mean age population is generally lower compared to European and Asian countries (especially China and Japan) (Wirdefeldt et al., 2011).

With regard to the European continent, the most recent review that investigated the PD prevalence in European countries was published by von Compenhausen et al. (2005), comprising 39 studies from ten countries, but Greece was not included. The highest prevalence of PD appeared in Germany, ranging from 713 to 12,500 per 100,000; whereas

the lowest (115/100,000) in Sweden (von Compenhausen et al., 2005). The literature search did not identify any publication for the prevalence of PD in Greece. However, according to the EPDA, the estimated number of PD patients in Greece, based on the prevalence rates in other European countries, are 23,439 (EPDA, no date).

The meta-analysis by Pringsheim et al. (2014) revealed that the prevalence rate of PD increases steadily with age, being extremely rare in those under the age of 50 years (41/100,000) and more common in individuals over 80 years (1903/100,000); probably due to the age-related changes in the neurotransmitter system, which may be responsible for the appearance of PD symptoms in older ages (Desai et al., 2010). The disease affects also mainly male population, and the reported male/female ratio ranges from 1/1 to 3/2 (de Lau and Breteler, 2006; Wirdefeldt et al., 2011). The less prevalence of PD in women and the later onset, could be explained by higher initial striatal dopamine (DA) levels in women, and the protective role of oestrogens against nigrostriatal degeneration (Miller and Gronin-Golomb, 2010).

### **3.3. Pathophysiology of Parkinson's disease**

PD is a neurodegenerative disorder that affects predominantly DA-producing neurons in the substantia nigra (SN), a specific area of the basal ganglia (BG). The BG are nuclei of the midbrain, within the hemispheres, part of the extrapyramidal system (Steiner and Tseng, 2010). Their main function is the motor control. In particular, they are involved in voluntary and automatic associated movements, and the suppression of unwanted movements. They contribute in regulating muscle tone, planning and initiating a movement, performing smooth movements, and learning movement patterns. In addition, they are functionally linked to emotional processing and cognition (Marsden and Obeso, 1994), and they are components of the central mechanism providing control of the lung ventilation (Kolesnikova, 2006).

The cerebral cortex, in order to initiate a voluntary movement, sends signals to the BG. In turn, the BG send signals back to the cortex, especially the motor cortex, via the thalamus. The signals from the cortex are sent to the spinal cord, and finally to the skeletal muscles for the performance of normal movement patterns. Within the BG, there are two pathways for the transmission and processing of signals from the cortex to thalamus: the direct and indirect pathway. The balance of activity between the two pathways is modulated by the neurotransmitter DA, which is released by the SN pars compacta to stratum (Steiner and Tseng, 2010).

In idiopathic PD, the reduced DA levels in the SN pars compacta, due to apoptosis or necrosis of dopaminergic neurons, are considered responsible for the onset of the disease. Due to the death of DA neurons, the DA action is lost, exciting the indirect pathway, which inhibits the movements; and inhibiting the direct pathway, which facilitates the movements. Thus, there is an alteration of the signals from the BG to thalamus, and there is no controlled normal movement pattern. The PD symptoms become apparent when the loss of the neuronal cell is around 80% (Hamani and Lozano, 2003).

Although the aetiology of the death of DA neurons is unknown, researchers have proposed some possible causes. For instance, mutations of the enzyme leucine-rich repeat kinase 2 may cause shortening and simplification of the dendritic trees; high concentration of oligomeric  $\alpha$ -synuclein protein may decrease DA release; and mitochondrial changes may lead to oxidative stress, which distorts the DA neurons, through the creation of free radicals (Surmeier et al., 2010). Although there is limited evidence so far, it is believed that environment factors; such as living and occupational exposure to some toxics may cause the aforementioned damages, which destroy the DA neurons (Noyce et al., 2012). In addition, mutations (mainly duplication or triplication) in some genes which encode proteins, might be related with the onset of PD (Nuytemans et al., 2010).

As the disease progresses, the degeneration extends beyond the SN. Neuron losses resulting in reduced acetylcholine (ACh), serotonin (5-HT), noradrenaline (NA) levels in

several areas of the central nervous system. The neurodegenerative process may affect specific parts of cortex, thalamus, brainstem, and spinal cord, as well as sympathetic and parasympathetic ganglia (Alexander, 2004).

A pathological hallmark that characterises PD is the presence of Lewy bodies, in the SN and other parts of the brain, such as in the raphe nuclei, hypothalamus, nucleus of Meynert, neocortex and cortex. Lewy bodies have never been identified in patients with other parkinsonian syndromes, apart from idiopathic PD. They are spherical, eosinophilic, cytoplasmatic, inclusions; which are composed of the protein  $\alpha$ -synuclein (40%), associated with other proteins, mainly ubiquitin. The function of Lewy bodies is under debate. They may represent either a destructive mechanism that initiate the death of DA neurons; or a protective mechanism of the surviving cells, by segregating and recycling errant proteins (Hamani and Lozano, 2003).

### **3.4. Symptoms of Parkinson's disease**

Despite the fact that PD is considered a movement disorder, it is characterised by both motor and non-motor symptoms. The progression differs among the patients; and there is a wide range of clinical heterogeneity of symptoms, maybe due to its complex pathophysiology and the affected damaged brain areas (van Rooden et al., 2011).

#### **3.4.1. Motor symptoms**

In most cases (46% to 85% of PD patients) there is an asymmetric presentation of motor symptoms in the early stages of the disease, maybe due to the unequal number of neurons in both sides of the SN in healthy population. However, symptoms become bilateral as the disease progresses (Maetzler et al., 2009). The main motor symptoms of PD are listed as follows:



- **Bradykinesia.** It is the most common clinical feature of PD, is defined as the reduced movement speed and amplitude. It is also characterised by increased reaction times (Heisters, 2011).
- **Tremor-at-rest.** A tremor is an uncontrollable shaking movement that affects a part of the body, due to alternating agonistic-antagonistic innervation of distal muscles. It usually affects the hands and lower limbs; and rarely the chin and lips. It appears to 70%-85% of PD cases, it occurs at a frequency between four and six Hertz at rest, and is often inhibited during the performance of voluntary movements (Heisters, 2011).
- **Rigidity.** Rigidity refers to the stiffness or inflexibility of the muscles, which prevent them from stretching or relaxing (Heisters, 2011). It is characterised by increased muscular resistance, usually accompanied by the “cogwheel” phenomenon. It may affect both extensors and flexors muscles (Jankovic, 2008). Rigidity may decrease the range of movement (ROM) of voluntary movements and lead to postural deformities, such as camptocormia<sup>1</sup> and Pisa syndrome<sup>2</sup> (Heisters, 2011).
- **Postural instability or balance impairment** refers to the difficulty in maintaining the upright position and stability in sitting or when transferring. It is generally a manifestation of the late stages of PD (three to five H&Y stages), and usually occurs after the onset of rigidity and bradykinesia (Kim et al., 2013).
- **Gait disturbances.** The two main characteristics of parkinsonian gait are freezing of gait (FOG) and festination. FOG typically manifests as a sudden and transient inability to move during specific situations: turning, under environmental constraints (e.g. walking through a narrow passage), and step initiation (Heisters, 2011). Festination describes the rest characteristics of parkinsonian gait; such accelerating steps with increased cadence, shorter stride, longer double support time, flat foot strike, and reduced arm swing (Morris et al., 2008).
- **Wearing-off.** It is a motor fluctuation, and is considered a complication of levodopa (L-dopa) therapy, in which the effects of L-dopa are diminished before it is time for the next dose. Thus, some types of dyskinesia<sup>3</sup> may arise. They can manifest as chorea and

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<sup>1</sup> Extreme flexion of the thoracolumbar spine

<sup>2</sup> Tilting of the trunk, particularly when sitting or standing

<sup>3</sup> Involuntary movements resulting in fragmented or spasmodic motions

dystonia, and rarely as athetosis. Dyskinesia is developed, on average about five years after starting L-dopa therapy, in 50% of patients (Caillava-Santos et al., 2015).

#### 3.4.2. Non-motor symptoms

A plethora of non-motor symptoms are present in PD, grouped in four categories: sensory, autonomic, cognitive-behavioural and sleep disorders (Pandya et al., 2008). The survey by Barone et al. (2009) revealed that 98.6% of patients with PD suffered from at least one non-motor symptom; with an average of 7.8 symptoms per patient. The causes of non-motor symptoms seem to be multifactorial; associated with the underlying pathophysiology of PD and/or being derived from the cardinal motor features (Chaudhuri and Schapira, 2009). The fact that some non-motor symptoms appear before the onset of motor symptomatology, may be explained by the Braak staging, which is a method to classify the pathological process in PD based on the distribution of Lewy bodies. The Braak staging supports that the degeneration does not start from the SN; but other brain areas are affected first, which may be responsible for the onset of some non-motor symptoms. (Braak et al., 2003). Depression is considered one of the most common non-motor symptoms in PD (section 3.6.1).

### **3.5. Impacts of Parkinson's disease**

#### 3.5.1. Falls and fall-related injuries

PD sufferers have three times greater risk of falls than similarly aged healthy individuals; probably due to the motor (e.g. postural instability and gait disturbances) and non-motor symptoms (e.g. orthostatic hypotension) of the disease (Rudzińska et al., 2013). Falls in PD are a leading cause of physical trauma, hospitalisation, disability, impaired QoL, and caregiver stress (Gazibara et al., 2014). Due to the high number of falls, the prevalence of hip fractures is four times higher in PD patients compared with age-matched controls (Melton et al., 2006).

### 3.5.2. Disability

PD is a leading cause of disability, as both basic activities of daily living (ADLs) (e.g. dressing, bathing) and instrumental ADLs (e.g. shopping, preparing food) are reduced even from the first stages of the disease. Among the motor symptoms; gait disturbances, postural instability, and bradykinesia have the strongest correlation with disability; whereas tremor-at-rest has no correlation (Muslimović et al., 2008). The disability is greater during the off-state, as the motor symptoms are less controlled (Shulman, 2010). A plethora of non-motor features have also strong correlation with disability, such as cognitive deficits and fatigue (Muslimović et al., 2008).

### 3.5.3. Social impacts

An additional impact is the loss and alteration of the individual's social identity<sup>4</sup>. The social impacts are not always related to the severity of the disease, as they depend on the disability arising from the disease's symptoms, emotional status and support by others. They may affect the working environment and the daily lifestyle (Soundy et al., 2014). For instance, patients gradually avoid going out to social events, due to the stigma arising from the signs of the disease; whereas dyskinesia seems to be the most embarrassing motor symptom. Hypophonia<sup>5</sup> impairs the participation in social networks and telephone conversation (Khlebtovsky et al., 2012). In addition, patients may be unable to retain a job, due to disability. Others reduce the number of working hours, or find an alternative job that is not as fast paced or physically demanding (Chiong-Rivero et al., 2011).

### 3.5.4. Reduced quality of life

The QoL in PD may be reduced even from the first stages of the disease. PD patients report diminished QoL levels when compared to healthy controls or other chronic disorders, such as multiple sclerosis and diabetes mellitus (Den Ouden et al., 2007). It seems that the QoL is affected by many factors; such as the signs of the disease and their impacts, socio-

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<sup>4</sup> Individual's knowledge that they belong to a certain social group

<sup>5</sup> Abnormally weak voice

demographic features, health status and adverse reaction to treatment. However, as some factors are connected via multiple pathways, it is difficult to report the determinants of reduced QoL in PD (Schrag, 2006).

#### 3.5.5. Hospitalisation and nursing home admissions

Although the hospitalisation due to PD is less frequent compared to other chronic disorders; the annual number of admissions seems to be higher in the advanced stages, maybe due to the complications of the disease (Vosius et al., 2010). The primary reasons for emergency hospital admissions are the non-motor symptoms of the disease and comorbidities, such as pneumonia and fall-related injuries (Braga et al., 2014). The average length of stay in hospitals varies from 2.3 (Mahajan et al., 2016) to 9.7 days (Braga et al., 2014). Following inpatient hospitalisation; there is an increased nursing home admission, due to disability and the lack of dependent care at home. However, additional strong predictors for nursing home admissions are dementia, hallucinations and psychosis (Safarpour et al., 2015).

#### 3.5.6. Financial cost

PD is considered one of the most costly chronic diseases, with high direct and indirect cost (Rodríguez-Blázquez et al., 2015). The total annual cost per capita in European countries ranges from 2,620 to 9,820 euros, whereas the direct cost ranges between 60% and 70% of the total cost (von Campenhousen et al., 2011). Differences in the cost of healthcare services, pharmacological treatment and taxies, and the services provided to patients and carers by the NHS; may explain the higher direct and indirect cost per capita in Western European than Eastern countries (von Campenhousen et al., 2011).

#### 3.5.7. Caregivers' burden

Caregivers of PD patients, especially those who are partners, experience a heavy physical and psychological burden (Secker and Brown, 2005). The determinants of caregivers' burden are: cognitive decline, mental disorder (anxiety, depression), sleep disorders, level

of disability, PD duration of patients, low social support and total period of caregiving. The depression and anxiety levels of caregivers of persons with PD are twice higher compared to their peers; whereas they experience diminished QoL (Santos-Garcia and de la Fuente-Fernandez, 2015).

### **3.6. Depression in Parkinson's disease**

#### **3.6.1. Prevalence rates of depression in Parkinson's disease**

Depression is the most common psychiatric complication affecting individuals with PD (Marsh, 2013). The systematic review by Reijnders et al. (2008) resulted that the prevalence rates of clinically significant depressive symptoms vary broadly across studies, ranging from a low 2.7% to a high of 89%, with a weighted mean of 35%. In addition, more recent experimental studies (Riedel et al., 2010; Perrin et al., 2017) and narrative reviews (Hemmerle et al., 2012) indicated that the most commonly cited prevalence of depression in PD is between 40% and 50%. These variations may reflect differences arising from the studies' methodology, such as: the patient selection procedures (inpatient/outpatient population), characteristics of the sample (sociodemographic characteristics and severity of PD), the assessment tools for the detection of anxiety and depression (rating scales or specific diagnostic criteria), the experience and qualification of assessors (psychologists or other healthcare professionals), and the types of depression included in each study (Reijnders et al., 2008).

In regard to the severity of depression and the types of depressive disorders in PD; it seems that the patients usually appear mild to moderate depressive symptoms, and occasionally severe (Marsh, 2013). The systematic review by Reijnders et al. (2008) revealed that 17% of the overall PD population suffers from major depressive disorder (MDD), 22% from minor depression, and 13% from dysthymia. Similarly, studies that used rating scales with cut-off values to assess the severity of depressive symptoms, showed that minor depression varies between 36.3% and 40.3%, whereas severe depression between 12.9% and 16.7% (Rojo et al., 2003; van der Hoek et al., 2011).

Current knowledge supports that PD patients experience higher rates of depression than individuals suffering from other chronic diseases, or when compared to controls (Marsh, 2013). One study (Veiga et al., 2009), showed that the prevalence of depression in individuals over 60 years was four times higher in PD (42%), when compared to age-matched controls (10%). Similarly, when PD is compared with other neurological diseases; the prevalence of depression in PD (20%-45%) is higher than in other neurological conditions, such as stroke (10%-34%) and multiple sclerosis (20%-25%) (Rickards et al., 2005; Hellmann-Regen et al. 2013). It is unknown whether the higher prevalence of PD depression is associated with more severe impacts of PD in patients' life, or whether it is related to the underlying pathophysiology of PD (Marsh, 2013).

### 3.6.2. Pathophysiology of depression in Parkinson's disease

There has been considerable debate over the aetiology of depression in PD, which is believed to be complex. Depression is a manifestation of the underlying disease process in PD (primary depression), and/or a 'reaction' of coping with a chronic, progressive and disabling disease (reactive or secondary depression) (Marsh, 2013). Symptoms of depression can predate the motor features and the clinical diagnosis of PD, even ten years before the diagnosis of PD (Bower et al., 2010). This could be supported by the Braak staging, as mood disorders may start at Braak stage two; when dysfunctions occur at locus coeruleus, which has connections to amygdala and hypothalamus. On the contrary, the motor symptoms appear at Braak stage three, when the degeneration affects the midbrain, especially the SN (Jacob et al., 2010).

Biological approaches support that the pathophysiological mechanisms implicated in PD depression include abnormalities in the system of neurotransmitters (Eskow Januarjs et al., 2011); whereas less evidence is available for the role of the hypothalamic–pituitary–adrenal (HPA) axis (Du and Pang, 2015). Regarding the neurotransmitters, as L-dopa may not reduce depression scores, it seems that not solely the dopaminergic system contributes to the onset of depression (Marsh et al., 2006). The phenotype of depression in PD reveals that the noradrenergic system is affected more, due to difficulties in concentration and

diminished attention (Eskow Januarjs et al., 2011). However, post-mortem and neuroimaging studies in depressed subjects with PD revealed that the dopaminergic and serotonergic system are also involved (Dissanayaka et al., 2014). With respect to the HPA axis, Du and Pang (2015) concluded that it may be a dysregulation in the HPA axis in PD, as Lewy bodies were detected in the pituitary lobe and adrenal glands. On the contrary, the hypothalamus was relatively free of body Lewy formation. In addition, DA deficits in the pituitary gland may disrupt its normal function and adrenocorticotrophic hormone (ACTH) secretion, activating the release of cortisol, causing stress and depressive symptoms (Du and Pang, 2015).

Depression may also be a result of the emotional dimensions of coping with a chronic, progressive disease; without cure and only symptomatic management (Marsh, 2013). Socio-psychological approaches focus on the role of psychological and social factors for the development of mental disorders in chronic somatic disease. The dominant models are: the psychodynamic, behavioural, cognitive and the sociocultural model. (Borrell-Carrió et al., 2004). The psychodynamic model, supports that the pathophysiology of mental disorders is caused by internal psychological factors, rather than biological, and the mechanisms of dysfunctions arise to conscious mind (Wasserman, 2011). The cognitive approaches support that dysfunctional thoughts lead to extreme emotions, which may lead to maladaptive behaviours (Weich et al., 2009). According to behavioural approaches, abnormal behaviour is learned; whereas the sociocultural approaches describe the psychopathology of mental disorders as the result of the interaction between the individuals and their cultures (Strongman et al., 1995). Indeed, in PD depressive symptoms may arise or worsen during the disease process by a variety of factors, such as: the motor fluctuations and off-periods, which lead to mood fluctuations; concerns about the disease and its impacts; perceived or actual disability; low social support; stigma; stereotypes about the disease; and PD cost (Marsh, 2013; Pachana et al., 2013).

### 3.6.3. Impacts of depression in Parkinson's disease

The presence of depression in patients with PD can worsen the impacts of the disease (Chapter 3.5); however the research in this field is limited so far. Although it is not clear whether the motor symptoms are a risk factor for the development of mental disorders, or if depression may worsen the motor symptoms of PD; Jankovic (2008) believes that bradykinesia may be dependent on the emotional state of the patient, due to 'kinesia paradoxa', a phenomenon where PD patients with akinesia<sup>6</sup> may be able to perform quick movements after they become excited. The contribution of PD depression in falls has been little studied. The study by Ashburn et al. (2001) revealed that higher levels of depressive symptoms are associated with increased number of falls. Perhaps, the antipsychotic medication and psychomotor slowing may increase gait instability and lead to falls (Iaboni and Flint, 2013).

With respect to disability, when PD depressed population was compared with non-depressed patients, the levels of disability were significantly higher in the depressed group; probably due to the loss of interest and fatigue, which may lead to physical inactivity (Pontone et al., 2016). Although PD depression has not been studied; in general population depression may result to social impacts; such as: diminished social activities, less working hours, unemployment or dismissal, reduced communication with family and friends, and lead to separation or divorce (Lépine and Briley, 2011). The presence of depression may increase further the economic burden of the disease, due to direct cost associated with antidepressant medication and psychotherapy (Lépine and Briley, 2011). One study that was held in Germany indicated that the direct cost was significantly higher in PD patients with depression; adding 1,142 euros to the annual cost of the disease (Winter et al., 2010).

In addition, the review by Den Ouden et al. (2007) indicated that depression is the strongest predictive value for poor QoL in PD. This is also confirmed by a more recent study, where depression accounted up to 31.5% of impairment in QoL scores (Liu et al., 2015). It seems that depressed PD patients, due to loss of interest and reduced motivation, cannot

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<sup>6</sup> Inability to start an act or motion



create strategies to cope with the difficulties arising from PD (Carod-Artal et al., 2007). Furthermore, the cohort study by Hughes et al. (2012) showed that depression is an important predictor of mortality in PD. Although the reasons of death were not explored further; it is believed that the hypercortisolaemia, due to the HPA hyperactivation, may redistribute body fat and increase blood pressure by decreasing insulin resistance, increasing the risk for coronary artery disease (Hughes et al., 2012). Lastly, the mental disorders seem to be a determinant factor for caregivers' burden in PD (Carod-Artal et al., 2013; Santos-Garcia and de la Fuente-Fernandez, 2015). In turn, the affected psychology of caregivers may have negative feedback to sufferers with PD, exacerbating the patients' symptoms of anxiety and depression (Scazufca et al., 2002).

#### 3.6.4. Diagnosis of depression in Parkinson's disease

The gold standard and the most widely used criteria for the diagnosis of depressive disorders are the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, and the International Statistical Classification of Diseases and Related Health Problems (ICD) criteria by psychologists using semi-structured clinical interviews (Jacob, 2006). The appendix 3.1 summarises the types of depressive disorders according to the DSM-IV criteria.

There are many barriers to the diagnosis of depression in the general population. Despite the fact that both biological and socio-psychological factors are considered responsible for the onset and development of depression, the diagnosis is only based on the symptoms and not on the aetiology of the disease (Avasthi and Ghosh, 2014). Although some laboratory tests –such as blood tests and magnetic resonance imaging- have been proposed for the diagnosis of MDD; they are not accepted diagnostic tools, and they cannot replace the DSM and ICD criteria. Their aim is to exclude medical conditions with similar symptoms or to identify deficits in some brain structures (Anderson et al., 2002; Verma et al., 2012). In addition, in semi-structured clinical interviews, the diagnosis is based on patients' responses and the symptoms they present, whereas some patients may cover consciously or unconsciously their depressive symptoms (Avasthi and Ghosh, 2014). In particular, males

may hide these symptoms, due to stereotypical perceptions about the role of men in society (Rochlen et al., 2009). Religious individuals may be skeptical about the role of mental health providers, may believe that depression is a part of life and does not necessarily require professional intervention (Bryant et al., 2013). The fear of stigmatisation in some societies hampers diagnosis and further management of depression (Nasir and Al-Qutob, 2005). Lastly, according to psychologists, the diagnosis is particularly problematic: in the elderly, patients with chronic somatic diseases, and individuals with a different cultural background, due to limited knowledge in these populations; and in patients with limited verbal skills, due to the inability to express their feelings (van Rijswijk et al., 2009).

Depression in PD may be even more under-recognised, and as hence, poorly treated (Marsh, 2013). Indeed, trials have shown that the percentage of depressed PD population receiving antidepressant medication varies from 8.6% to 35% (Weintraub et al., 2003; Hemmerle et al., 2012). The reasons for its under-recognition are multifactorial. Firstly, PD patients and caregivers are less likely to report the non-motor symptoms to their physician; as they might be embarrassing, or they ignore that they may be related to their disease (Chen and Marsh, 2014). Furthermore, apathy, which often accompanies PD, may decrease motivation to seek help (Pachana et al., 2013). Secondly, non-expert neurologists may do not have the ability to recognise and diagnose neuropsychiatric symptoms (Chen and Marsh, 2014), probably due to diagnostic imprecision; and complexity of diagnosis, as some symptoms of depressive disorders overlap with PD symptoms or may be considered part of aging (Pandya et al., 2008). However, one study revealed that 67% of PD patients with a previous confirmed diagnosis of depression, were detected as depression-free, despite the fact that they were examined by experts using the DSM criteria (Bouwman and Weber, 2012). This revealed the limitations of diagnostic criteria to detect depression in PD population, as patients with PD may do not meet the criteria for defined subtypes of depression according to the DSM criteria (Rickards, 2005).

Thus, the assessors should also be aware of the phenotype of PD depression, which seems to be qualitatively different from depression in general population. Some classical symptoms of depression, such as psychotic symptoms in MDD, guilty, sadness, anhedonia, suicidal ideation, and changes to appetite may be less frequent in PD depression. On the contrary, common reported depressive symptoms among the PD population include: low energy, difficulties with concentration, making decisions and hopeless (Ehrt et al., 2006; Farabaugh et al., 2009).

### 3.6.5. Management of depression in Parkinson's disease

The management of depression in PD includes pharmacotherapy, psychotherapy and supplementary treatments; such as the electroconvulsive therapy (ECT), bright light therapy (BLT), acupuncture and physical activity (Chapter 4).

The antidepressant medication in PD does not differ from those types of drugs administrated in overall depressed population; including: serotonin–norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and atypical antidepressants (Marsh, 2013). Drug trials in PD depression have assessed classical antidepressants as well as antiparkinsonian medication used to treat the motor symptoms of PD. The antidepressant contributions of L-dopa and DA agonists antiparkinsonian drugs have not been well established yet, even in cases that the motor features of PD were improved (Barone, 2011; Eskow Jaunarajs et al., 2011). With regard to the antidepressant drugs; SSRIs and TCAs have been more studied in PD, whereas less evidence is available for SNRIs. The antidepressant effects of all these drugs, when compared to placebo, are modest; but there are some studies with significant short-term results (Costa et al., 2012). However, when antidepressants are administrated in PD patients, special caution is needed. Both SSRIs and TCAs are known for their anticholinergic effect, which may exacerbate PD-associated non-motor symptoms, such as cognitive disturbances. In addition, SSRIs may cause extrapyramidal side effects, such as tremor (Muller, 2012). Lastly, the combination of SSRIs with monoamine oxidase B (MAO-B) inhibitors may precipitate

the 5-HT syndrome; which is characterised by high body temperature, agitation, tremor, sweating and diarrhea (Wishat and Macphee, 2011).

The application of psychological approaches for the treatment of PD depression has received little experimental attention, whereas the cognitive-behavioural treatment (CBT) is the most studied approach (Chen and Marsh, 2013). However, more evidence is needed to conclude if the CBT is effective in alleviating depressive symptoms, especially about the long-term effects (Armento et al, 2012). Similarly, more evidence is needed to establish the effects of ECT, BLT and acupuncture in depressed population with PD. Although they appear to be effective treatments for PD depression, the evidence is provided by a small number of studies, which lacked randomisation (Troeng et al., 2013; Cumper et al., 2014; Zeng and Zhao, 2016).

### **3.7. Summary of Chapter 3**

- PD is the most common movement disorder, and the second most common neurodegenerative disease after Alzheimer's disease.
- The reduced DA levels in the SN pars compacta, due to apoptosis or necrosis of dopaminergic neurons, are considered responsible for the onset of the PD.
- PD has several impacts, such as: increased number of falls, disability, social impacts, reduced QoL, high direct and indirect cost, and caregiver's burden.
- Although PD is considered a movement disorder, it is characterised by both motor and non-motor symptoms.
- Depression is one of the most common non-motor symptoms of the disease affected about 35% of patients with PD.
- The pathophysiology of depression in PD is complex, and it seems that both biological and psychosocial factors contribute to its onset and development.
- Although there is limited evidence, it seems that the presence of depression in PD population may worsen the impacts of PD.

- The findings about the effects of antidepressant and antiparkinsonian drugs on depression in PD are controversial; whereas more research is needed to establish the effects of CBT, ECT, BLT and acupuncture.

# **CHAPTER 4**

## **SYSTEMATIC REVIEW**

#### **4.1. Introduction**

The high prevalence of PD, the increased levels of depression in this population, and their impacts are well-established (Chapter 3). In addition, the effectiveness of therapeutic exercise as an adjunctive treatment for PD, and the clinically anxious and depressed population has been a popular research topic over the last two decades. Thus, the current systematic review aimed to synthesise, critically evaluate all the available evidence, and conclude whether physical activity is an effective treatment in reducing anxiety and depression scores in PD. As an essential component of the evidence-based practice is the transformation of theory into practice; an objective was to suggest the best exercise parameters to clinicians, based on the selected trials with significant outcomes at the end of the treatment.

#### **4.2. Rationale for the systematic review**

Evidence arising from reviews, regarding the effectiveness of exercise in anxious and depressed moods among PD patients is lacking. Previous systematic reviews and meta-analyses have mainly focused on the motor aspects of the disease and QoL. To date, five systematic reviews (Goodwin et al., 2008; Adamson et al., 2015; Lamotte et al., 2015; McNeely et al., 2015; Cusso et al., 2016) have partially examined the effects of exercise to alleviate anxiety and depression in patients with PD. Of these systematic reviews, only the review by Cusso et al. (2016) included anxiety as an outcome of interest.

Adamson et al. (2015) examined the role of exercise in depression among patients with neurological disorders, including PD patients. Although the review was published recently, it included only two relevant RCTs in PD. The other reviews (Goodwin et al., 2008; Lamotte et al., 2015; McNeely et al., 2015; Cusso et al., 2016) focused only on PD population. However, as depression and anxiety were examined as part of the non-motor symptoms of PD; the discussion in this area was limited. Two reviews (Lamotte et al., 2015; Cusso et al., 2016) did not involve only RCTs, resulting in systematic reviews of non-high level of evidence. Furthermore, Lamotte et al. (2015) assessed only endurance (aerobic) exercise training; whereas McNeely et al. (2015) just dance interventions. Lastly, Cusso et al. (2016)

did not exclude occupational therapies interventions, in which exercise was just a component of the whole intervention. Although the findings of the reviews were inconclusive; physical activity was proved to be effective to some degree in improving emotional well-being. However, they failed to detect the most effective type of exercise and its parameters in PD population with comorbidity anxiety and depression.

### **4.3. Research aim, objectives and question**

#### **4.3.1. Research aim**

As no previous systematic review focused solely on the effects of therapeutic exercise on anxiety and depression in PD sufferers; the aim of this review was to summarise and evaluate all the relevant available RCTs, identify gaps, and propose directions for future research.

#### **4.3.2. Research question**

The research question of the review could be formulated as follows:

*“Based on the selected trials, could therapeutic exercise significantly reduce anxiety and depression levels in PD population?”*

#### **4.3.3. Research objectives**

The research objectives of the current review were:

- To conclude if therapeutic exercise could reduce anxiety and depressive symptoms in PD population, and whether the effects persist after the end of the intervention period.
- To identify the most effective evidence-based type of exercise and its parameters; such as exercise intensity, frequency, and total intervention period.
- To report the safety of therapeutic exercise programmes in this population.



#### **4.4. Selection of the appropriate review design**

Between the 14 types of reviews that appear in scientific magazines and assist in the update of evidence-based practice (Grant and Booth, 2009), a systematic review was selected for the current thesis; because it is a scientific method for identifying, evaluating and synthesising large bodies of evidence from primary studies. It also appraises the risk of bias within individual studies, and identifies gaps for future research. As it is based on pre-defined methods, there are less possibilities for bias arising from the review (Grant and Booth, 2009; Hoffmann et al., 2013). Systematic reviews are also recommended in the field of physiotherapy to examine the effects of interventions and assist treatment decisions (Linde and Willich, 2003). However, a meta-analysis approach was rejected, after the identification of all relevant trials; because they were considered to be heterogeneous with respect to study population, types of interventions, groups of comparison, and measurement tools. In this case, a quantitative analysis may lead to misleading results; and only a qualitative synthesis is proposed (Hoffmann et al., 2013).

#### **4.5. Material and methods**

##### **4.5.1. Design of the systematic review**

The current systematic review was conducted in accordance with the recommendations and criteria as outlined in Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) to minimise bias and errors (Moher et al., 2009). The process of study selection, data extraction, quality assessment of selected studies, and data analysis was undertaken by two independent reviewers -the PhD student (TC) and the leader PhD supervisor (AY)-. At the end of each step, the reviewers compared their findings, and disagreements between them were resolved by discussion, as recommended by Aveyard (2007). However, there was no need for a third reviewer to make the final decision, as recommended by Torgerson (2003); because agreement reached 100% after discussion.

#### 4.5.2. Eligibility criteria

The eligibility criteria were determined based on the population, intervention, comparison, outcome and study design (PICOS) approach (Aveyard, 2007). To be included within the review, studies had to fulfill the following criteria:

##### *Study design*

Only RCTs were selected, due to their high level of evidence (Torgerson, 2003). Their design was parallel to facilitate the comparison between the study groups. RCTs with delayed start design or crossover design were excluded, except the cases where the first period was analysed as a parallel group trial. No restrictions were placed regarding the year of publication, to evaluate the whole amount of research done in this area and to indicate any changes over the years (Glasziou et al., 2001). Only full-text articles, published in scientific magazines, were included; whereas abstracts, summaries, congress reports, dissertations and unpublished studies were excluded. Abstracts and summaries were excluded, because some key points or details of the whole procedure may be missed; congress reports and dissertations, due to limitation of time. Unpublished studies were not included, as some parts of the study may have not been completed yet, and may be changed up to the publication day. Finally, only articles written in English were selected, as the involvement of an official translator to translate the articles would extend the duration of study and increase its cost.

##### *Population*

Individuals with PD, irrespectively of their age and disease severity were included. PD should had been confirmed by a neurologist/specialist or/and by the use of well-accepted diagnostic criteria. There were not any restrictions whether the sample population was diagnosed with clinical levels of anxiety or/and depression, using accurate diagnostic tools.

### *Intervention*

The intervention could be any type of exercise -conventional or alternative-. RCTs in which the exercise was given as a part of a treatment (e.g. multidisciplinary rehabilitation), or in conjunction with other treatments (e.g. exercise and CBT) were excluded, because it is not possible to know how each component contributed to the results. The exercise programme could be conducted either in the intervention group (IG) or the comparison group (CG) of the study. Studies that examined the effects of a single exercise bout were excluded, as the current review aimed to examine only the training effects of exercise. The follow-up, could be no exercise or any other intervention.

### *Comparison*

The comparison interventions could be one of the following: (a) no intervention or usual care, (b) exercise, (c) other treatment (e.g. CBT), (d) same exercise intervention plus an additional treatment (e.g. exercise plus education).

### *Outcome measures*

The selected papers included at least one outcome (anxiety or depression), to measure the response to treatment. Anxiety and/or depression were either the primary or secondary outcome measures of the study. The measurement tools could be either patient-reported outcome measures (PROMs) or clinician-reported outcome measures (CROMs). Only studies that measured anxiety and depressive symptoms – at baseline and at the end of the intervention- separately from other mood symptoms were included. Trials reporting overall mood disturbances and those with combined measurements of anxiety and depression were excluded, unless they reported depressive and anxiety symptoms separately.

### 4.5.3. Search strategy for identification of studies

#### *Electronic (internet) searching*

Two main computerised literature searches were carried out: a preliminary search and a main search. The preliminary search was conducted in March 2015 without any restrictions to identify all the relevant research papers, and examine whether the methodology and results of the non-RCTs and non-English published papers were similar with those RCTs written in English language. This procedure ensures limited possibilities for publication bias (Glasziou et al., 2001).

The main search consisted of two steps: the first between 24<sup>th</sup> and 29<sup>th</sup> April 2015; and the second -an updating of the literature- on 29<sup>th</sup> November 2016. During the first search, studies were searched from the inception of databases until 24<sup>th</sup> April 2015; and during the second search, from 1<sup>st</sup> January 2015 to 29<sup>th</sup> November 2016. Some limiters (e.g. English language, humans, clinical trial) were selected to restrict the literature. A broad range of areas including sports, exercise, psychology and health literature, were searched. The literature search was carried out on 11 electronic databases: AMED, ASSIA, CINAHL, Cochrane Central Register of Controlled Trials, EMBASE, MEDLINE, PsycINFO, PEDro, PubMed, Scopus and SPORTDiscus. Keywords were structured using the PICOS approach and are presented in table 4.1 (p. 37). Although exercise is a subcategory of physical activity (Pate, 1988), in the literature, the terms 'exercise' and 'physical activity' are used interchangeably (Caspersen et al., 1985). Thus, for the purpose of the present study, both terms were used to capture conventional and alternative types of exercise; such as dance, Tai Chi and yoga. The keywords were applied using the Boolean operators "AND" (to combine keywords of two different columns) and "OR" (to combine keywords of the same column).

**Table 4.1.** Keywords applied for the electronic strategy regarding population, intervention and outcomes.

Population	Intervention	Outcomes
Parkinson's disease	Physical activity	Anxiety
Parkinson*	Exercise	Depression
PD	Physiotherapy	Anxious
	Physical therapy	Depressive
	Rehabilitation	Mood
	Occupational therapy	Emotional well-being
	Aerobic training	
	Anaerobic training	
	Resistance training	
	Strength training	
	Balance training	
	Cue* training	
	Dance	
	Tango	
	Yoga	
	Tai Chi	
	Qigong	
	Martial arts	

### *Hand searching*

Hand searching was conducted to identify papers that were not identified through electronic searching. Available journals that were most likely to yield the relevant trials were searched (Torgerson, 2003). This procedure was performed on 31<sup>st</sup> July 2015 at the Library of the General Hospital of Athens 'Evangelismos'. Only two Greek Physiotherapy magazines, that include some articles in English language, were found and searched: 'Φυσικοθεραπεία' (Fysikotherapeia) (from January 1982 to April-May-June 2015) and 'Θέματα Φυσικοθεραπείας' (Themata Fysikotherapeias) (from January 2002 to May 2003).

### *Cross referencing*

When all the studies were collected, their references were checked to identify further relevant articles that may have been missed (Sim and Wright, 2000; Haidich, 2010).

Additionally, the references of the previous systematic reviews (Goodwin et al., 2008; Adamson et al., 2015; Lamotte et al., 2015; McNeely et al., 2015; Cusso et al., 2016) in the given area were checked to identify additional missing studies (Torgerson, 2003).

#### 4.5.4. Study selection

There was no blinding to studies' author(s), place of publication or results during the eligibility assessment. However, unblinded reviewers may have prejudices on this information (Holly et al., 2012). Duplicated articles were excluded. In turn, titles and abstracts were screened to exclude irrelevant articles. If this was not clear, the full-length articles were read carefully to determine whether the eligibility criteria were met (Torgerson, 2003).

#### 4.5.5. Data extraction

A data extraction form was designed to record the key points of each study and facilitate the comparison of the selected RCTs (Torgerson, 2003) (Appendix 4.1).

#### 4.5.6. Quality assessment

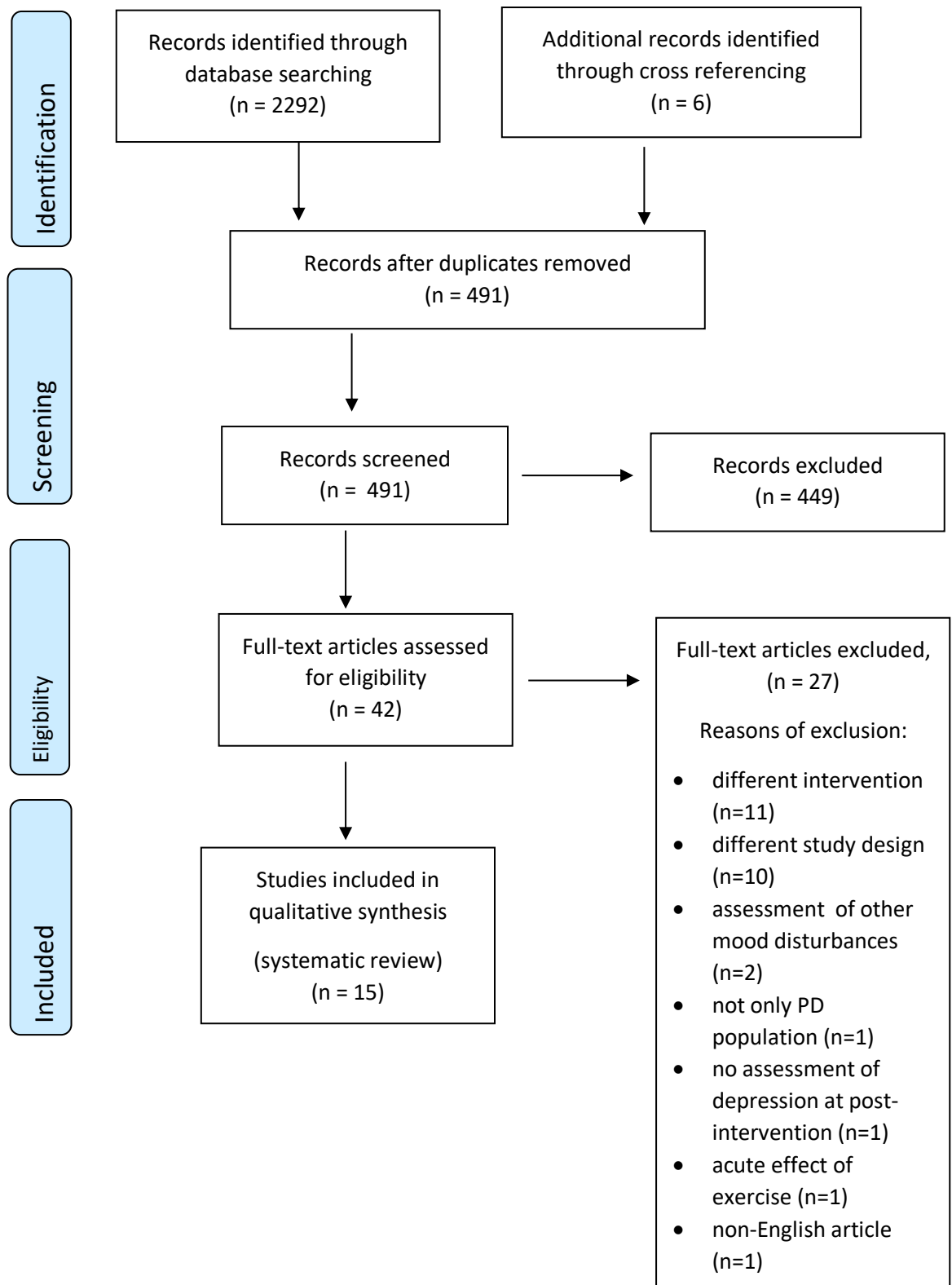
The methodological quality of the selected RCTs was rated using the Physiotherapy Evidence Database (PEDro) scale, which is designed for physiotherapy and exercise studies (Foley et al., 2006). The PEDro scale is simple without multiple items and complex scoring system, and quick to complete it. It is also valid and reliable measure of methodological quality (Maher et al., 2003; Foley et al., 2006). A brief description of the PEDro scale and the quality appraisal tool form are presented in Appendices 4.2 and 4.3 respectively. Studies scoring nine and ten were considered to be of 'excellent' quality, from six to eight of 'good' quality, from four to five of 'fair' quality, and up to three of 'poor' quality' (Maher, 2000; Foley et al., 2003). In the current thesis, similar to the systematic review by Adamson et al. (2015) and the PEDro guidelines, the seven criterion was not satisfied when self-reported scales were used for the assessment of anxiety and depression. In trials in which

key outcomes are self-reported, the assessor is considered to be blind if the subject was blind to the group allocation (Sherrington, 2000).

## **4.6. Results**

### **4.6.1. Selection process**

The flow of trials through the selection process is presented in figure 4.1 (p.40). Overall 2298 papers were retrieved by electronic searching and cross referencing; none by hand searching. Of the 42 full-text articles; 27 were excluded, as they did not meet the exclusion criteria (Appendix 4.4). Finally, 15 studies were deemed to be eligible for the review (Bridgewater and Sharpe, 1996; Burini et al., 2006; Schmitz-Hubsch et al., 2006; Modugno et al., 2010; Smania et al., 2010; Shulman et al., 2013; Nadeau et al., 2014; Cugusi et al., 2015; Dashtipour et al., 2015; Hashimoto et al., 2015; King et al., 2015; Rios Romenets et al., 2015; Schlenstedt et al., 2015; Sharma et al., 2015; Teixeira-Machado et al., 2015).



**Figure 4.1.** Systematic review's flow diagram.



#### 4.6.2. Methodological quality

The methodological quality of the selected trials is presented in table 4.2. All of them scored between three and six, with a mean score of 4.64 (fair quality). The PEDro criteria most frequently satisfied were: random allocation of subjects to study groups (criterion two), and similar baseline comparability of groups regarding the most important prognostic indicators (criterion four). On the contrary, unblinded subjects, therapists and assessors (criteria five to seven) were present in all the RCTs.

**Table 4.2.** Methodological quality assessment of included studies using PEDro scale.

First author name (year of publication)	PEDro Criteria											Total score	Methodological quality
	Eligibility criteria	Random allocation	Concealed allocation	Baseline comparability	Blinded subjects	Blinded therapists	Blinded assessors	Adequate follow-up	Intention-to-treat-analysis	Between group comparisons	Point measures and variability		
Bridgewater (1996)	1	1	0	1	0	0	0	0	0	1	1	4/10	fair
Burini (2006)	0	1	1	1	0	0	0	0	0	1	1	5/10	fair
Cugusi (2015)	1	1	0	1	0	0	0	0	0	1	1	4/10	fair
Dashtipour (2015)	1	1	0	1	0	0	0	1	0	1	1	5/10	fair
Hashimoto (2015)	1	1	1	1	0	0	0	0	0	1	1	5/10	fair
King (2015)	1	1	1	1	0	0	0	1	0	1	1	6/10	good
Modugno (2010)	1	1	0	1	0	0	0	0	0	0	1	3/10	poor
Nadeau (2014)	1	1	1	1	0	0	0	0	0	1	1	5/10	fair
Rios Romenets (2015)	1	1	0	1	0	0	0	0	1	1	1	5/10	fair
Schlenstedt (2015)	0	1	0	1	0	0	0	0	1	1	1	5/10	fair
Schmitz-Hubsch (2006)	1	1	0	1	0	0	0	1	1	1	1	6/10	good
Sharma (2015)	1	1	0	1	0	0	0	1	0	1	0	4/10	fair
Shulman (2013)	1	1	0	1	0	0	0	0	0	0	1	3/10	poor
Smania (2010)	1	1	0	1	0	0	0	1	0	1	1	5/10	fair
Teixeira-Machado (2015)	1	1	0	1	0	0	0	1	1	1	0	5/10	fair

It is interesting that the criterion one (eligibility criteria) was not satisfied in two studies (Burini et al., 2006; Schlenstedt et al., 2015), because the source of subjects was not described. Although the criterion four (baseline comparability) was satisfied in all the trials, three RCTs (Bridgewater and Sharpe, 1996; Schmitz-Hubsch et al., 2006; Sharma et al., 2015) did not report baseline comparison for depression between the study groups. In five trials (Burini et al., 2006; Modugno et al., 2010; Nadeau et al., 2014; Dashtipour et al., 2015; King et al., 2015), the baseline scores, between the study groups, differed significantly on measures of depression and anxiety. Regarding the criterion eight (adequate follow-up), only six trials (Burini et al., 2006; Modugno et al., 2010; Nadeau et al., 2014; Hashimoto et al., 2015; King et al., 2015; Schlenstedt et al., 2015) outlined reasons for drop-out up to the end of the study. The combined results of these studies are presented in table 4.3. It seems that the reasons for drop-out were not related to the exercise programme itself. Lastly, despite the fact that one point was awarded in criterion ten, seven trials did not provide between-group statistical comparison for depression and anxiety (Bridgewater and Sharpe 1996; Burini et al., 2006; Schmitz-Hubsch et al., 2006; Smania et al., 2010; Shulman et al., 2013; Nadeau et al., 2014; Sharma et al., 2015).

**Table 4.3.** Reasons for drop-outs.

Reasons for drop-outs	Number of subjects
Medical reasons: pain in joints and injuries*	31
High number of absences	12
Family demands	7
Changes in PD medication	6
Missed or refusal to participate in the final assessment	5
Moving to another city	5
Unwilling to participate in the study	4
Hospitalisation	2
Transportation difficulties	2
Discomfort with exercise	2
Disappointment not being selected to the intervention (exercise) group	2
Participation in another training programme during the study period	1
No clear explanation	1

\* not during the exercise session

### 4.6.3. Study characteristics

#### *Study methods*

Four trials (Schmitz-Hubsch et al., 2006; Modugno et al., 2010; Rios Romenets et al., 2015; Sharma et al., 2015) were pilot studies. Of the remaining 11 studies, pilot-work before the main study was conducted only in the study by Hashimoto et al. (2015).

#### *Population*

The trials comprised an aggregate of 535 participants at baseline; 58.97% of them were males. Although sample population consisted only of PD patients; the Argentine tango partners in the IG by Rios Romenets et al. (2015) were healthy volunteers, which were not assessed and included in the results. The basic participants' characteristics are summarised in table 4.4 (p. 45). A sample size calculation was not necessary for the four pilot studies (Schmitz-Hubsch et al., 2006; Modugno et al., 2010; Rios Romenets et al., 2015; Sharma et al., 2015). Of the 11 remaining trials, only four (Smania et al., 2010; Hashimoto et al., 2015; King et al., 2015; Schlenstedt et al., 2015) reported sample size calculations.

#### *Intervention*

The basic interventions' characteristics are summarised in tables 4.5 (p. 46) and 4.6 (pp. 47-48). Across all the studies, the exercise interventions were clinically heterogeneous in terms of exercise mode, and all the exercise parameters. Both conventional and alternative forms of physical activity were performed; such as dance, yoga and Qigong. Aerobic training was the most common type of exercise used by five studies (Bridgewater and Sharpe, 1996; Burini et al., 2006; Shulman et al., 2013; Nadeau et al., 2014; Cugusi et al., 2015). All the interventions were carried out indoors, apart from Nordic walking (Cugusi et al., 2015). Exercise intensity was reported only in the studies that used aerobic training or dance as intervention (Bridgewater and Sharpe, 1996; Burini et al., 2006; Shulman et al., 2013; Nadeau et al., 2014; Cugusi et al., 2015; Hashimoto et al., 2015). The intensity was expressed either as a percentage of an individual's maximum heart rate ( $HR_{max}$ )<sup>7</sup> or heart

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<sup>7</sup>  $HR_{max}=220 - \text{age in years}$

rate reserve (HRR)<sup>8</sup>. Based on the classification of exercise intensity (Appendix 4.5), it could being assumed that the exercise intensity was mainly moderate (ACSM's, 2006).

### *Comparison*

The exercise intervention was compared with two groups only in four studies (Shulman et al., 2013; Nadeau et al., 2014; Hashimoto et al., 2015; King et al., 2015). In nine trials (Burini et al., 2006; Smania et al., 2010; Shulman et al., 2013; Nadeau et al., 2014; Dashtipour et al., 2015; Hashimoto et al., 2015; King et al., 2015; Rios Romenets et al., 2015; Schlenstedt et al., 2015), the IG was evaluated against another exercise training programme. The comparison is presented in table 4.6 (pp. 47-48).

### *Outcomes*

The outcomes relevant to anxiety and depression are summarised in table 4.7 (p. 49). All the selected trials (n= 15) reported depression as an outcome measure, whereas, only one (Dashtipour et al., 2015) assessed anxiety. All measures of anxiety and depression, besides the Hamilton Depression Scale (HAM-D) (Modugno et al., 2010) and the Montgomery-Asperg Depression Rating Scale (MADRS) (Schmitz-Hubsch et al., 2006), were self-reports scales. Only six trials revealed significant improvements at the end of the treatment, using within-group comparison tests (Smania et al., 2010; Nadeau et al., 2014; Cugusi et al., 2015; Hashimoto et al., 2015; King et al., 2015; Teixeira-Machado et al., 2015).

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<sup>8</sup> HRR= HRmax – resting heart rate (HRrest)

**Table 4.4.** Characteristics of included RCTs (participants).

First author name and year of publication	Country	Participants				
		Sample size	Gender (%)	Mean age (in years)	Mean time since diagnosis (in years)	H&Y stage (All)
Bridgewater (1996)	Australia	26	M: 61.5 F: 38.5	IG: 67.3 CG: 66.5	IG: 4 CG: 4	1-3
Burini (2006)	Italy	26	M: 34.6 F: 65.4	IG: 65.7 CG: 62.7	IG: 11.2 CG: 10.6	2-3
Cugusi (2015)	Italy	20	M: 80 F: 20	IG: 68.1 CG: 66.6	IG: 7 (median) CG: 7 (median)	1-3
Dashtipour (2015)	USA	11	M: 45.6 F: 54.4	IG: 62.8 CG: 64	IG: 2.9 CG: 4.5	IG: 1.3 (mean) CG: 1.8 (mean)
Hashimoto (2015)	Japan	46	M: 26.1 F: 73.9	IG: 67.9 CG1: 62.7 CG2: 69.7	IG: 6.3 CG1: 7.8 CG2: 6.9	2-4
King (2015)	USA	58	M: 41 F: 59	IG: 64.6 CG1: 64.3 CG2: 63.9	IG: 5.2 CG1: 7.9 CG2: 5.4	2.4 (mean)
Modugno (2010)	Italy	20	M: 50 F: 50	IG: 63.2 CG: 62	IG: 9.5 CG: 9.4	2-4
Nadeau (2014)	Canada	34	M: 79.4 F: 20.6	IG: 64.0 CG1: 60.1 CG2: 64.3	N/A	1.5-2
Rios Romenets (2015)	Canada	33	M: 57.6 F: 42.4	IG: 63.2 CG: 64.3	IG: 5.5 CG: 7.7	1-3
Schlenstedt (2015)	Germany	40	M: 65.6 F: 34.4	IG: 75.7 CG: 75.7	IG: 10.1 CG: 9.3	2.5-3
Schmitz-Hubsch (2006)	Germany	56	M: 76.8 F: 23.2	IG: 64 CG: 63	IG: 6 CG: 5.6	Any stage of disease
Sharma (2015)	USA	13	M: 46.2 F: 53.8	IG: 62.8 CG: 73.4	IG: 3.2 CG: 3.7	1-2
Shulman (2013)	USA	67	M: 74.6 F: 25.4	IG: 66.1 CG1: 65.8 CG2: 65.3	IG: 5.9 CG1: 6.3 CG2: 6.3	1-3
Smania (2010)	Italy	55	M: 52.7 F: 47.3	IG: 67.6 CG: 67.3	IG: 10.4 CG: 8.6	3-4
Teixeira-Machado (2015)	Brazil	30	N/A	IG: 60.7 CG: 61	N/A	2-3

Abbreviations. CG: comparison group; F: female; H&Y: Hoehn and Yahr; IG: intervention group; M: male; N/A: not available; USA: United States of America.

**Table 4.5.** Characteristics of included RCTs (intervention- first part).

First author name and year of publication	Intervention				
	Type of exercise	Exercise protocol	Setting	Exercise format	Supervision
Bridgewater (1996)	Aerobic training	warm-up: ROM & strengthening main part: walking with music cool-down: stretching	Hospital	N/A	Supervised
Burini (2006)	Aerobic training	Warm up: 10 minutes cycle ergometer of low intensity Main part: 30 minutes cycle ergometer Cool down: 10 minutes cycle ergometer of low intensity and stretching	Neuro-rehabilitation facility	Group	N/A
Cugusi (2015)	Aerobic training	warm-up main part: Nordic walking cool-down	City park	Group	Supervised
Dashtipour (2015)	LSVT BIG therapy	Large trunk and extremity functional motions	University	N/A	Supervised
Hashimoto (2015)	Dance	Modern dance using elements from aerobic, jazz, tango and classical ballet	N/A	N/A	N/A
King (2015)	ABC home-based Exercise	6 stations: tai chi, boxing, pilates, lunges, kayaking, agility course	Home	Individualised	Unsupervised
Modugno (2010)	Multimodal exercise	warm-up: breathing & stretching exercises main part: postural, walking & balance exercises cool-down: passive mobilisation, coordination & breathing exercises	N/A	Individualised	Supervised
Nadeau (2014)	Aerobic training (speed TT)	warm-up main part: treadmill walking; initial speed at 80% of preferential walking speed ↑ speed by 0.2 km/h per session cool-down	University	Individualised	Supervised
Rios Romenets (2015)	Dance	Traditional Argentine tango for beginners. No special techniques for PD beginners. Encouragement to participate in 'milongas' after the dance class and socialise with other dancers.	Dance studio	Group	Supervised
Schlenstedt (2015)	Resistance training	warm-up main part: lower limbs exercises using body weight, weight cuffs & elastic bands as resistance; 3 sets of 15-20 repetitions per exercise cool-down	N/A	Group	Supervised
Schmitz-Hubsch (2006)	Qigong	Selected exercises from four groups, as described in the book of Guorui (2000)	N/A	Group	Supervised
Sharma (2015)	Yoga	Iyengar Hatha programme Warm-up: breathing and relaxation techniques Main part: 5-8 yoga poses Cool-down: meditation plus recommended yoga training at home	University	Group	Supervised
Shulman (2013)	Aerobic training	Higher-intensity treadmill exercise	Medical centre	N/A	Supervised
Smania (2010)	Balance training	10 exercises of 5-10 repetitions grouped in 3 categories: self-destabilisation, externally induced destabilisation, destabilising activities	University	Individualised	Supervised
Teixeira-Machado (2015)	Feldenkrais method-based exercise	Breathing, flexibility, balance and strengthening exercises; position changes; relaxation	Hospital	N/A	Supervised

Abbreviations. ABC: Agility Boot Camp; LSVT: Lee Silverman Voice Therapy; N/A: not available; PD: Parkinson's disease; ROM: range of motion; TT: treadmill training.

**Table 4.6.** Characteristics of included RCTs (intervention-second part- and comparison)

First author name and year of publication	Intervention				Comparison	
	Programme duration (in weeks)	Exercise sessions per week	Session length (in minutes)	Exercise intensity	Type of comparison	Description of protocol
Bridgewater (1996)	12	2	40 - 55	65%-85 % HRmax	'Internet talks' on health issues	Once every 3 wk
Burini (2006)	7	3	45	50%-60% HRR	Qigong	Group exercise, sessions of 50 min, 3 times per wk
Cugusi (2015)	12	2	60	60%-80% HRR	No intervention	N/A
Dashtipour (2015)	4	4	60	N/A	Multimodal exercise	Treadmill & trunk and upper limb exercises; 4 60-min sessions per wk; exercise intensity: 75% HRmax for treadmill, and up to 5 on Borg scale for limb exercise.
Hashimoto (2015)	12	1	60	50%-70% HRmax	Multimodal exercise (CG1)	Warm-up: ROM exercises; main part: balance training, walking, transfers; cool-down: stretching and breathing exercises; one 60-min session per wk; exercise intensity: 50%-70% HRmax
					No intervention (CG2)	N/A
King (2015)	4	3	60	N/A	Individualised exercise programme (CG1)	ABC programme; similar to the IG, but supervised; 3 60-min sessions per wk.
					Group exercise programme (CG2)	ABC programme; similar to the IG, but in groups and supervised; 3 60-min sessions per wk.
Modugno (2010)	156 (3 years)	3	90	N/A	Active theatre	Vocal and therapeutic exercises, and staging; up to 12 hours per month
Nadeau (2014)	24	3	60	up to 75% HRmax and BP up to 200 mm Hg	Mixed TT (CG1)	Similar to the IG, but ↑1% treadmill incline and 0.2 km/h treadmill speed alternately; 3 60-min sessions per wk.
					Viactive programme (CG2)	Exercises based on tai chi, latin dance, elastic band & coordination movements; low intensity; 2 60-min group supervised sessions & 1 60-min. home unsupervised session per wk
Rios Romenets (2015)	12	2	60	N/A	Home-based exercise	Daily individualised exercise based on a booklet by the PSC entitled 'Exercise for people with Parkinson's'
Schlenstedt (2015)	7	2	60	Moderate	Balance training	Self-destabilisation and externally induced destabilisation in different directions; 2 60-min sessions per wk
Schmitz-Hubsch (2006)	24 (8 wk exercise - 8 wk pause - 8 wk exercise)	1	60	N/A	No intervention	N/A

First author name and year of publication	Intervention				Comparison	
	Programme duration (in weeks)	Exercise sessions per week	Session length (in minutes)	Exercise intensity	Type of comparison	Description of protocol
Sharma (2015)	12	2	60	N/A	No intervention	N/A
Shulman (2013)	12	3	15-30	from 40%-50% HRmax to 70%-80% HRR	Lower-intensity treadmill (CG1)	15-50 min up to 40%-50% HRR; 3 sessions per wk
					Stretching and resistance (CG2)	Resistance exercises of lower limbs using resistance machines, and stretching of the trunk and lower limbs; 3 sessions per wk
Smania (2010)	7	3	50	N/A	Multimodal exercise	ROM, muscle stretching & motor coordination exercises; 3 50-min sessions per wk
Teixeira-Machado (2015)	24	2	60	N/A	Educational lectures	Instructions for the prevention of falls, PD medication, management of the ADLs; 1 per wk

Abbreviations. ABC: Agility Boot Camp; ADLs: activities of daily living; CG: comparison group; HRmax: maximum heart rate; HRR: heart rate reserve; IG: intervention group; min: minutes; N/A: not available; PSC: Parkinson Society of Canada; ROM: range of motion; TT: treadmill training; wk: weeks.



**Table 4.7.** Characteristics of included RCTs (outcomes).

First author name and year of publication	Outcomes					
	Outcome measure	Primary or secondary outcome	Assessment tool	Mid-term results	Post-intervention results	Follow-up results
Bridgewater (1996)	D	N/A	LPDQ		N/A	(4 weeks post-intervention) IG: SI; CG: NSI
Burini (2006)	D	primary	BDI		IG: NSI CG: NSI	
Cugusi (2015)	D	primary	BDI-II		IG: SI CG: NI	
Dashtipour (2015)	D & A	N/A	BDI BAI		D: SI (all) A: NSI (all)	(12 weeks post-intervention) D: SI (all); A: SI (all) (24 weeks post-intervention) D: SI (all); A: NSI (all)
Hashimoto (2015)	D	N/A	SDS		IG: SI CG1: NSI CG2: NSI	
King (2015)	D	secondary	GDS		IG: NSI CG1: SI CG2: NSI	
Modugno (2010)	D	secondary	HAM-D	(1 year after the start) IG: NI; CG: NSI (2 years after the start) IG: NI; CG: SI	IG: NI CG: SI	
Nadeau (2014)	D	secondary	BDI-II	(12 weeks after start) IG: SI CG1: NSI; CG2: NI	IG: SI CG1: NSI CG2: NSI	
Rios Romenets (2015)	D	secondary	BDI		IG: NSI CG: NSI	
Schlenstedt (2015)	D	secondary	BDI		IG: NSI CG: NSI	(4 weeks post-intervention) IG: NSI; CG: NSI
Schmitz-Hubsch (2006)	D	secondary	MADRS	(12 weeks after start) N/A	Reductions in both groups	(24 weeks post-intervention) Reductions in both groups
Sharma (2015)	D	secondary	GDS	(6 weeks after start) N/A	IG: NSI CG: N/A	(6 and 12 months post-intervention) N/A
Shulman (2013)	D	secondary	BDI		IG: NI CG1: NSI CG2: NI	
Smania (2010)	D	secondary	GDS		IG: SI CG: NI	(4 weeks post-intervention) IG: NSI; CG: NI
Teixeira-Machado (2015)	D	primary	BDI		IG: SI CG: NI	

A: anxiety; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; BDI-II: Beck Depression Inventory-II; CG: comparison group; D: depression; GDS: Geriatric Depression Scale; HAM-D: Hamilton Depression Rating Scale; IG: intervention group; LPDQ: Levine-Pilowsky Depression Questionnaire; MADRS: Montgomery-Asperg Depression Rating Scale; NI: no improvement (from baseline); N/A: not applicable; NSI: non- significant improvement from baseline ( $p > .05$ ); SDS: Zung self-rating Depression Scale; SI: significant improvement from baseline ( $p < .05$ ).

#### 4.6.4. Effective exercise types and parameters

The current section looked solely at the trials that reported exercise to be effective (either in the IG or CG), in order to recommend the type and the specific dosage parameters of exercise to improve anxiety and depressive symptoms in PD. The exercise characteristics of these studies are summarised in Appendix 4.6.

### **4.7. Discussion**

#### 4.7.1. Findings and interpretation

To our knowledge, this is the first systematic review focusing solely on the effectiveness of physical activity interventions on anxiety and depression in PD population. This is surprising, as anxiety and depression are among the most prevalent non-motor symptoms in PD (Goldman and Postuma, 2014), which may worsen the impacts of the disease. In addition, growing evidence suggests that physical activity is an effective intervention for depression, and probably for anxiety, in general population; and it could be a viable adjunct treatment in combination with pharmacological and psychological management. (Bartley et al., 2013; Schuch et al., 2016a; Schuch et al., 2016b).

In the current systematic review, fifteen studies fulfilled the eligibility criteria and included in the analysis. In spite of anxiety being one of the most common non-motor symptoms in PD (Goldman and Postuma, 2014), only one relevant study (Dashtipour et al., 2015) was identified. On the contrary, all the experimental studies focused on depressive levels, but in a non-clinically depressed population. Despite the fact that anxiety and depression were rarely examined as primary endpoints, the vast majority of selected studies ( $n=13$ ) showed positive findings in the reduction of depressive symptoms at the end of physical activity intervention. These findings are promising, as exercise programmes are less expensive than pharmacological and psychological approaches, and have fewer side effects and contraindications than pharmacotherapy (Wenger et al., 2014). In turn, six studies revealed significant improvements ( $p<.05$ ) in depression scores at post-intervention. However,

there is insufficient evidence to support whether the improvement gained at post-intervention was sustained in the follow-up period.

Perhaps, the most important finding of this systematic review is the increasing interest of RCTs to evaluate psychological morbidities in the field of therapeutic exercise in PD since 2010. However, the heterogeneity of interventions in terms of exercise modality and exercise parameters, made the comparison between the selected studies difficult. Despite the fact that the literature supports that aerobic training is the most antidepressant type of exercise (Kvam et al., 2016), a variety types of physical activity were used. Indeed, conventional (aerobic, anaerobic, combined exercise), alternative types of physical activity (dance, Qigong, Yoga), and prescribed exercise programmes (LSVT BIG, ABC, Feldenkrais, Viactive) were applied either to the intervention or the comparison group. In turn, the trials utilised different exercise parameters in terms of duration, frequency, intensity, exercise format and supervision. Although walking outdoors is a recommended type of exercise in depressed populations (Kvam et al., 2016), only one relevant study (Cugusi et al., 2015) was identified. This was maybe due to the difficulty of standardising environmental conditions (temperature, humidity rates) and the intensity, when exercising outdoors (Perraton et al., 2010).

Even when only the effective studies were examined ( $p < .05$ ) (Smania et al., 2010; Nadeau et al., 2014; Cugusi et al., 2015; Hashimoto et al., 2015; King et al., 2015; Teixeira-Machado et al., 2015), the dissimilarities of training programmes, in conjunction with the limited number of RCTs and the methodological flaws; made it difficult to determine the superiority of any type of exercise and its parameters on PD anxiety and depression. Indeed, five of six effective trials (table 4.2, p. 41) were only of 'fair' quality, with a high number of methodological flaws, which may lead to several types of bias (section 4.7.3). Furthermore, as depression was examined as a secondary outcome, the findings may reflect chance. Thus, it was not possible to provide strong and precise recommendations for clinical settings. This information is vital to the clinicians who are considering physical activity as a treatment of comorbidity depression and anxiety in PD. However, the limited

data support that both conventional and alternatives types of physical activity, indoors or outdoors training, individualised or group approaches, short and longer periods of exercise (four to 24 weeks), with a frequency from one to three times a week, and duration of each session no longer than one hour, are associated with significant antidepressant effects at post-intervention. The fact that both individualised and group-based programmes significantly reduced depression, may support the theory that both biological and psychological mechanisms for the reduction of depressive symptoms, work in a complex and combined way, apart from the 'social interaction hypothesis', which is supported in group-based training programmes (Paluska and Schwenk, 2000).

In addition, the studies that reported the drop-out reasons, revealed that physical activity is a safe approach without adverse effects for the participants. Indeed, none of the training programmes was harmful for the patients, as none injury due to exercise was reported. It seems that both conventional and alternative types of therapeutic exercise, community-based and home-based, group and individualised approaches, highly supervised and non-supervised programmes are safe. Perhaps a strict screening procedure to assess the ability for participation, the design of the protocol and advice by experienced professionals ensure the safety of patients mildly or moderately affected by PD to a therapeutic exercise programme.

#### 4.7.2. Strengths of included trials

The major advantage of the included trials was that all of them were RCTs, providing high level of evidence, and eliminating selection bias (Evans, 2003). Although, the criterion two of the PEDro scale is satisfied even if the precise method of randomisation is not reported, it was unclear whether some experimental studies followed quasi-randomised allocation procedures for the allocation of participants to the study groups. Furthermore, as the sample population consisted of both males and females, there was low risk for gender bias (Ramasubbu et al., 2001). Although women are more likely to participate in research (Newington and Metcalfe, 2014), the fact that males were more than females in the majority of studies, ensures that the sample was representative of the overall population.

Similarly, the recruitment of outpatients increases the external validity of the trials, as the majority of patients mildly or moderately affected by PD live at their own homes.

Despite the fact that the clinimetric properties of the selected tools to assess anxiety and depression were not reported in the articles; the reviewers identified that both reliable and validated measurement tools, recommended in PD population, were used for identifying depression and screening its severity (Torbey et al., 2015) (see section 8.7.8 for more information). However, the self-reported Levine-Pilowsky Depression Questionnaire (LPDQ), used in one study (Bridgewater et al., 1996), is considered a valid and reliable tool for screening depression in general population (Carr and Smith, 1985), but there is no evidence for its clinimetric properties in PD population. Concerning anxiety, the Beck Anxiety Inventory (BAI) is a 'suggested' tool for anxiety in PD, because basic information about its validity and reliability in PD population is missing (Leentjens et al, 2011). However, there is not any recommended scale to assess anxiety in PD (Leentjens et al., 2008) (see section 8.7.8 for more information).

#### 4.7.3. Methodological flaws and limitations of included trials

The selected trials appeared several methodological flaws and limitations. The most significant limitation is that anxiety and depression were not assessed as primary outcomes in the majority of trials. Thus, the exercise intervention may not have been designed to alleviate anxiety and depressive symptoms in patients with PD, and the findings may reflect chance (Freemantle, 2001). In addition, no information was provided about the antidepressant and anxiolytic pharmacological treatment during the study period; and whether the subjects were receiving adjunct treatment to depression and anxiety, such as CBT. Thus, it is unclear whether other factors, apart from the intervention, influenced the anxiety and depression scores up the end of the treatment. These limitations were also present even in studies where depression was one of the main outcome measures.

In addition, the exercise protocol was not described thoroughly in 11 articles; and some crucial information -such as the number of participants in group-based programmes, the environmental conditions of exercise- were missing. Similarly, a large proportion of studies insufficiently described the treatment in the CGs. This information is vital to clinicians who are considering physical activity as a treatment for comorbidity depression and anxiety in PD.

An additional important weakness was that the experimental studies were not focused on individuals with clinical levels of anxiety and depression; but in non-anxious and non-depressed populations. None of the included studies reported a confirmed clinical diagnosis of anxiety or depression using accurate diagnostic criteria for mental disorders, such as the DSM and ICD criteria; or clinical levels of anxiety and depression, using relevant rating scales with cut-off scores. The effectiveness of training programmes in anxiety and depressive scores could differ, if only PD patients with diagnosed anxiety and depressive disorders were included in the studies (Wu et al., 2017).

With respect to the study design, four of 15 trials were pilot studies (Schmitz-Hubsch et al., 2006; Modugno et al., 2010; Rios Romenets et al., 2015; Sharma et al., 2015). Although pilot studies provide valuable data regarding feasibility and clinical effectiveness, the use of a small sample could lead to instability of the outcomes, making it harder to generalise to the whole population, affecting the external validity. Furthermore, it is quite likely that the method could be modified after the pilot work, in order to reach the objectives of the larger main study (Leon et al., 2011). Apart from the pilot studies, the majority of the included studies had been conducted on relatively small samples, without sample size calculations. Due to the small group size, there are increased possibilities for type I error<sup>9</sup>; and caution is needed for the generalisation of results (Faber and Fonseca, 2014).

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<sup>9</sup> The rejection of a true null hypothesis

In addition, in some studies the PEDro criteria two to nine were not fulfilled. Hence, the trials were highly susceptible to bias. In particular, the lack of allocation concealment increased the possibilities for selection bias (Altman and Schulz, 2001). The imbalance between groups in baseline scores of depression may have influenced the outcomes and weakened the trial's credibility (Roberts and Torgerson, 1999). Lack or inadequate reported blinding procedure, may have led to performance bias. As the participants were not blinded to the group allocation, the effect of the treatment could be due to placebo or Hawthorne effect<sup>10</sup>. Unblinded therapists could have also affected the results, due to therapists' enthusiasm or lack of enthusiasm for the treatment or control conditions. However, because of the nature of the exercise interventions, participants could never be blinded to the intervention, and neither the therapists; and therefore a score of eight out of ten could be considered a maximum score in these trials (Perraton et al., 2010). There were also high possibilities for assessor bias, as the criterion seven was not fulfilled in the selected studies, which used clinician-rated scales to assess depression (Day and Altman, 2000). Although the selected self-reported tools were both valid and reliable in PD population, there is danger for response bias; as the findings were based on subjects' answers, which may be inaccurate. The high loss to follow-up in nine included trials may have led to attrition bias, affecting studies' validity, because patients lost to follow-up often have a different prognosis than those who complete the study (Dettori, 2011). Lastly, an intention-to-treat analysis was not performed in 11 trials; hence, clinical effectiveness may have been overestimated (Hollis and Campbell, 1999).

In some studies, there were also serious limitations in the presentation of results for anxiety and depression, probably because they were tested as secondary outcomes. Indeed, some studies lacked information about the results at post-intervention or at follow-up; few presented the results for the whole sample, and not for each group separately; others did not report whether the improvements were significant or not, as probably the non-significant differences are less reported in the articles. In some cases, there were no within- and between-group comparisons for the measures of anxiety and depression. Hence, these studies may have omitted or modified outcomes, leading to outcome

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<sup>10</sup> Modification in subjects' behaviour, because they know they are being observed

reporting bias. In addition, the effect size was not reported –in all the selected trials- to assess the importance of findings (Pallant, 2016). Lastly, the majority of trials did not report the mean scores before and after treatment; preventing the reviewers to detect whether there were any clinically significant changes within the groups, based on the minimal clinically important difference (MCID).

Even in studies with significant results at post-intervention, there was lack of the interpretation of findings. The possible mechanisms of exercise -biological and psychological- which may have contributed to these results were not reported. This may partly be explained by the fact that anxiety and depression were examined as secondary outcomes. Only two studies (Smania et al., 2010; Hashimoto et al., 2015), which found significant improvements in depression scores at post-intervention, interpreted their results. It was hypothesised that the social interaction with peers may have contributed to the reduction of depressive symptoms. In addition, Smania et al. (2010) suggested that the improvement in depression symptoms resulted from the increased confidence in balance related to daily-life activities, and the decrease in the number of falls.

#### 4.7.4. Comparison with previous reviews

The results of the current review were consistent with previous systematic reviews and meta-analyses (Goodwin et al., 2008; Adamson et al., 2015; Lamotte et al., 2015; McNeely et al., 2015; Cusso et al., 2016) on the effects of exercise on anxiety and depressive symptoms in PD population. The above mentioned reviews indicated that conventional and alternative types of physical activity may reduce depressive levels; however, the majority of the included experimental studies did not reveal significant effects. Regarding anxiety, only the review by Cusso et al. (2016) included one relevant RCT, which examined the effectiveness of an occupational therapy programme in PD. Furthermore, no data was provided about the methodological quality of the selected trials using a valid critical appraisal tool. In addition, our review found more relevant experimental studies than the previous reviews, published in the same time period, indicating possible publication bias in the previous reviews.



However, before the submission of the current thesis, a relevant systematic review (Wu et al., 2017) was published in 2017. The review by Wu et al. (2017), which included nine studies, found that physical activity interventions have the potential to lessen depressive symptoms, even if they were assessed as secondary outcomes. Both conventional and alternative types of physical activity (e.g. Tai Chi and Yoga) were effective, particularly the implementation of aerobic exercise. On the contrary, it is unsure whether exercise had any effect on anxiety.

The results of the present review were in line with those by Wu et al. (2017), which appears several limitations. In particular, it included both studies of experimental and quasi-experimental design, having higher possibilities for selection bias (Torgerson, 2003). The literature search was limited from 2006 to 2017; hence, it did not indicate any changes over the years (Glasziou et al, 2001). In addition, in some included studies, the physical activity intervention was combined with an additional treatment; thus, it was not possible to know how each component contributed to results. The methodological quality of the selected studies was assessed by the modified Jadad scale. Despite the fact that the Jadad scale and its modified version, are two simple appraisal tools for clinical trials, and the most widely used worldwide; they have received negative criticism in the field of physiotherapy and exercise. As this scale was not originally developed for physiotherapy studies; it focuses only on randomisation, blinding, and dropouts to evaluate methodological quality of primary research; rather than concealed allocation and treatment adherence, which are important issues in physiotherapy (Olivo et al., 2008). Therefore, the Jadad scale provides a less comprehensive measure of methodological quality than the PEDro scale (Bhogal et al., 2005); and does not distinguish studies of 'low' quality from those of 'high' quality. In addition the scale has only been validated in the field of pain (Olivo et al., 2008).

#### 4.7.5. Strengths of the current review

The current systematic review was unique, because it was the first that focused solely on the effects of therapeutic exercise on anxiety and depression in patients with PD. A systematic manner was followed, as proposed by the PRISMA statement, for the selection

and critical appraisal of relevant studies (Hoffmann et al., 2013). This procedure, in conjunction with the previous experience of both reviewers in systematic reviews; ensured that many sources of bias, arising from the way a review is conducted, were kept to a minimum (Aveyard, 2007). In addition, the PEDro scale provided a comprehensive measure of methodological quality of the physiotherapy literature. Apart from the blinding component; it assessed the methodological quality of studies based on other important criteria; such as concealed allocation, intention-to-treat analysis, and adequacy of follow-up (Olivo et al., 2008). Lastly, the review provided useful information about the safety of exercise on this population, which should be considered in the clinical setting.

#### 4.7.6. Limitations of the current review

The current review was not free of limitations. Firstly, the decision to include articles written only in the English language, and to not locate and obtain relevant studies in the 'grey literature', may have led to publication and language bias (Chalmers and Altman, 1995). This decision was driven by the need to deliver the review on time, and to not increase the financial cost in case of translations. Regarding, the language of publication, there is empirical evidence that trials with statistically significant results are more likely to be published in English than in non-English language journals (Egger et al., 1997). However, the initial search identified only one relevant trial written in Portuguese (Christofolletti et al., 2012).

Similarly, studies with positive results are more likely to be published; while unpublished literature and 'grey literature' are more likely to include negative outcomes. These sources may be difficult to be identified when not indexed in electronic databases (Banks, 2004). Hence, possible eligible trials with non-significant or negative results may have not been included in this review. In addition, despite the extensive literature search, the reviewers may have not succeeded in identifying all the relevant experimental studies, leading to publication bias (Chalmers and Altman, 1995). Lastly, the reviewers were not blinded to studies' author(s), place of publication or results during the eligibility assessment, the data extraction procedure and the quality assessment of the selected trials. Unblinded

reviewers may introduce bias into systematic reviews, as they may produce significantly higher scores in the included trials, compared to blinded assessors (Jadad et al., 1996).

#### 4.7.7. Proposals for future research

Since this review cannot make any firm conclusions of the effectiveness of exercise for PD patients with comorbid anxiety and depression, and as there is an increasing interest in the field of evidence-based practice; there is need for future research in this area. Future studies should examine anxiety and depression as primary outcomes. It is advisable for future research to use rigorous scientific methodology through adequate samples following power calculations, concealed allocation, satisfactory randomisation procedures, adequate blinding, between groups comparisons and report of measures of variability. The use of clinician-administrated rating scales for the measurement of anxiety and depression may satisfy the assessors' blinding to the participants' group allocation. In addition, factors that may affect the scores of depression and anxiety at the end of the treatment should be excluded (e.g. CBT) or kept stable (e.g. antidepressant medication) through the whole study period. A rigorous methodology will eliminate the risk of bias, and both the internal and external validity of the studies will be higher.

To answer the question whether exercise is effective on improving anxiety and depression scores in patients with PD, future studies should focus on populations with clinical levels of anxiety and depression. The detection of anxiety and depressive disorders could be achieved either using the ICD and DSM criteria, the 'gold standard' for the diagnosis of mental disorders (Jacob, 2006); or recommended rating scales for this purpose (Torbey et al., 2015).

In addition, the design of the exercise protocols should be focused on the primary objectives of the study; and incorporate elements from previous experimental studies, reviews, clinical guidelines and recommendations for PD population and depressed or anxious population. Both conventional and alternative types of physical activity, indoors

and outdoors training could be tested. In PD, there is an increasing interest in the role of alternative exercise programmes. It is believed that they fill the gap left by conventional exercises, which does not always directly target enjoyment and social participation. In the general population, evidence supports that alternative forms of exercise are associated with higher adherence and continuation of these activities after the end of the intervention period (Alves da Rocha et al., 2015).

The comparison of at least two different training programmes would detect the type of exercise and the parameters that produce the largest antidepressant and anxiolytic effects in PD, determining the optimal dose of exercise. Evidence is also needed for the effectiveness of exercise when compared to other treatments, such as CBT; or combined approaches, such as exercise and CBT. Therefore, the healthcare system will be able to offer to the patients the best treatment and choice with the minimum cost.

The majority of studies are focused to explore statistically significant differences using appropriate statistical tests. However, there is more to research than just obtaining statistical significance. Thus, it is recommended to calculate the effect size in order to assess the importance of findings (Pallant, 2016), and confidence intervals to describe the precisions (Moher et al., 2010). In addition, researchers should explore whether there are clinically significant differences between the groups and changes within the groups. Lastly, patients' satisfaction could be explored to detect whether there are subjective improvements on mood due to intervention (Al-Abri and Al-Balushi, 2014; Porter, 2008).

Future studies should also examine both the short- and longer-term effects of physical activity interventions. They should also report data on adverse events, as this information is important in clinical populations where safety is an important consideration. Finally, assuming that exercise is beneficial for reducing anxiety and depressive symptoms, possible mechanisms of action may be of interest.

#### 4.8. Conclusion

To our knowledge, this review is the first to assess the evidence about the effectiveness of exercise interventions in anxiety and depressive symptoms in PD. The role of physical activity in this area has received little, but increasing attention over the years within existing literature. To date, it is not possible to determine exactly how effective physical activity is in reducing anxiety and depressive symptoms in clinical and non-clinical anxious and depressive populations with PD, and whether the effects persist after the end of the intervention period. In addition, only one RCT has assessed the anxiety scores so far. Due to the small number, heterogeneity and limitations of studies with significant results; it was not possible to provide relevant recommendations to clinician physiotherapists. Hence, future experimental studies with a rigorous methodology should fill the gap in the literature. However, it is encouraging that physical activity is safe for this population; as no injury was reported due to exercise, and none left the intervention, because it was harmful or boring.

#### 4.9. Summary of Chapter 4

- The aim of the present systematic review was to assess the effects of physical activity on anxiety and depression levels in PD population.
- The review was conducted according to the PRISMA statement, and the PEDro scale was used to assess the methodological quality of selected trials.
- 11 electronic databases were searched to identify relevant articles.
- 15 RCTs fulfilled the eligibility criteria and included in the analysis. All the studies assessed depression, and only one anxiety.
- The selected trials scored between three and six, with a mean score of 4.64.
- Although there is some evidence that exercise could reduce PD depression, it is not possible to draw firm conclusions and provide recommendations; due to the methodological flaws of studies and heterogeneity among the exercise parameters.
- Despite the fact that only six trials outlined reasons for drop-out; therapeutic exercise programmes seem to be safe in this population.

- Future experimental studies with rigorous methodology should focus on the effectiveness of exercise on PD patients with clinical levels of anxiety and depression.

# **CHAPTER 5**

## **SURVEY - METHODOLOGY**

### 5.1. Introduction

The survey aimed to identify the impacts of PD on everyday activities and emotional status in patients with PD in Greece. The answers of participants would be considered for the design of the group-based therapeutic exercise and educational programme of the present RCT, in order to meet their needs. A mixed mode survey was conducted using online and paper questionnaires. Initially, an online survey was designed. However, due to low response rate, it was decided to deliver additional paper questionnaires to reach the required sample size.

### 5.2. Study aim and design

#### 5.2.1. Aim of the study

The aim of the survey was to detect and list the impacts of PD on everyday activities and emotional status in patients with PD in Greece. The record of these data, in combination with the socio-demographic characteristics and the health status of the patients; would provide an in depth understanding of the target population, and the most prevalent responses would be considered for the design of the group-based therapeutic exercise and educational programme of the current thesis.

#### 5.2.2. Research questions

Based on the study's aim, the research questions were formulated as follows:

1. *"What are the most prevalent restricted ADLs in Greek PD population?"*
2. *"What are the most common emotional disturbances in Greek citizens with PD?"*

#### 5.2.3. Research objectives

The objectives of the survey were listed as follows:

- a) The design of a disease specific questionnaire to record the socio-demographic characteristics, health status, physical and mental health in Greek PD population.



- b) To record personal beliefs about their experience living with PD. This information may support further the need for the design of a rehabilitation programme in PD.

#### 5.2.4. Research design

A survey was considered the appropriate research design, because it is a method of gathering information from a sample, without comparing different groups (Iarossi, 2006). Surveys do not infer cause-and-effect by manipulating variables. They are designed to describe or explain phenomena, and provide an early understanding about clinical conditions or situations, without making judgment (de Leeuw et al., 2008; Salaria, 2012). Thus, they are recommended in healthcare studies to begin a research in a new area, and assess the health status of communities (Grimes and Schulz, 2002). Regarding the type of survey, a questionnaire was selected to gather the relevant information, as it is cheaper and quicker than interviews (Iarossi, 2006; Rea and Parker, 2014).

### **5.3. The research team**

#### 5.3.1. Members and responsibilities

Eight professionals participated in the current project, which were recruited from the HPDA, apart from the translator and the physiotherapist who participated in the qualitative analysis. All of them were healthcare professionals, volunteers of the HPDA, with previous experience in PD. Their duties are reported in table 5.1 (p. 66).

#### 5.3.2. Training of volunteers

One training session with all the professionals was performed to inform them about the purpose of the study and their responsibilities. The standard operating procedure (SOP) for the online survey, including the link for the online questionnaire, was sent to them by e-mail. An updated SOP and the paper-based questionnaire were also sent for the paper survey. In addition, the volunteer (nurse), who participated in the paper survey, was present during the first meeting of the principal researcher with the respondents, to have a general overview about the whole process.

**Table 5.1.** Professionals' duties.

Qualification	Duties	Number of professionals
Principal Researcher (PhD student)	Design of the study, delivery of paper surveys, data analysis	1
Psychologist	<ul style="list-style-type: none"> <li>• Consignment invitation and reminder e-mails to the members of the HPDA for the online survey</li> <li>• Post announcements on the official webpage and Facebook page of the HPDA for the online and paper survey.</li> </ul>	1
Nurse	Delivery of the paper questionnaire to respondents, in case of principal researcher's absence.	1
Neurologist	Selection of items for the questionnaire.	1
Physiotherapists		2
Translator	Translation of the questionnaire from Greek to English	1
Physiotherapist	Qualitative analysis	1

Abbreviations. HPDA: Hellenic Parkinson's disease Association.

## 5.4. Participants

### 5.4.1. Eligibility criteria

The respondents were included whether the following criteria were met:

1. Individuals with PD, members of the HPDA and residents of Greece; irrespectively of their gender, nationality, age, disease duration and stage; or carers of PD patients (e.g. caregivers, relatives).
2. Respondents able to read and write in Greek, as the self-administrated questionnaire was written in the Greek language.
3. Adequate vision and hearing (hearing only for the paper questionnaire) –with or without special equipment-, in order to be able to complete the questionnaire and communicate with the researcher, if needed (Iarossi, 2006).

Respondents were excluded if:

1. They were unable to provide consent, due to cognitive impairment or other cause (Iarossi, 2006).
2. The patients were diagnosed with parkinsonism or other extrapyramidal syndrome, because the RCT would include just population with idiopathic PD.

#### 5.4.2. Sample size determination

The sample size was determined by the equation proposed by Hicks (2009):

$$N = P_y P_n / (\text{standard error})^2,$$

where  $P_y$  and  $P_n$  are the expected answers to questions, and  $N$  is the required number of participants. As there was no expectation of how the respondents would respond to questions, and the direction of responses was completely unknown; a 50/50 split was assumed. Therefore, both  $P_y$  and  $P_n$  were equal 0.5. The usual acceptable sampling error in research is 5% or 0.05. To obtain the standard error in the above equation using a 5% error limit and 95% confidence, 0.05 was divided by 1.96, which is equal to 0.025 (Hicks, 2009). Thus, entering the values in the formula yields:

$$N = 0.5 \times 0.5 / 0.025^2 \rightarrow N = 384.16 \approx 384$$

Therefore, a total of 384 people were defined as the required sample. As the initial survey was online, and the average response rate in web surveys is 34 % (Shih and Fan, 2008); the invitation had to be sent -via e-mail- to at least 1130 individuals.

#### 5.4.3 Recruitment of participants

The respondents were recruited from the HPDA. On October 2013, the HPDA had 1254 enrolled members and about 1500 followers on facebook. The enrolled members were: PD patients, caregivers or relatives of PD patients, and individuals who wanted to get informed about PD and the actions of the organisation. The HPDA contacts its members only through e-mails, as the online enrollment with the HPDA does not require a telephone number and a home address. The analytical recruitment process is provided in Sections 5.8.3 and 5.8.4.

## 5.5. Design of the questionnaire

The previous relevant literature and similar questionnaires found on the internet, were consulted for the design of the current questionnaire (Boynton and Greenhalgh, 2004). At each step, the strengths and weaknesses of relevant experimental studies and recommendations were weighted against each other to reach a final decision, which would be the best for the purpose of the current survey. As both an online and a paper-based questionnaire were designed for the current survey; this section analyses the design of both types of questionnaires.

### 5.5.1. Mode of administration

A self-administrated questionnaire was preferred instead of a questionnaire completed by the interviewer. In self-administrated questionnaires, there is more privacy and time to complete the questionnaire (McDonald, 2012); and the respondents may recheck their answers before the final submission (Jenn, 2006). In addition, they may decrease the non-response percentage in sensitive questions (Krumpal, 2013). As a main disadvantage of self-administrated questionnaires is that the researcher is usually unaware if the questionnaire was filled in by the respondent (Rattray and Jones, 2007); in the current survey the individual who completed the questionnaire had to select whether he/she was a PD patient or a carer of a PD patient.

### 5.5.2. Method of delivery

There are three main methods for the delivery of the questionnaires to the target population: phone-, paper- and internet-based surveys (de Leeuw et al., 2008). A phone-based method was immediately declined, as the HPDA has not the telephone numbers of its members. An internet-based method was preferred instead of a paper-based survey. Internet questionnaires may reach very large audiences in different areas of the country inexpensively. They provide a wide range of time until the deadline for the questionnaires' submission (Deutskens et al., 2004; de Leeuw et al., 2008). They are associated with relative rapid replies, as the average response time is 5.59 days (Ilieva et al., 2002). Furthermore,

even the senior population in Western countries is familiar with the use of internet, and there is a relative high level of computer literacy (Rea and Parker, 2014). Finally, the HPDA has a list with all the e-mails of its members. Between the two forms of internet based-survey; a web (online) survey was preferred, instead of an e-mail survey. Online surveys, sending people a link to a web page containing a questionnaire, which is filled in online, are generally quicker, easier to complete and submit than e-mail surveys (Wright, 2005).

Paper questionnaires was the 'plan B' to continue the survey, in case of low response rates of the internet survey (plan A). Although paper questionnaires are associated with higher cost (e.g. printing the forms), they have higher response rates than the internet surveys (Yetter and Capaccioli, 2010). Between the different forms of paper-based surveys, a mail (post) survey was declined for several reasons. The mail survey is associated with higher cost, including a stamped, pre-addressed return envelope; and the average response time is long (12.21 days) (Ilieva et al., 2002). In addition, the HPDA does not have the home addresses of its members. Hence, a face-to-face method was selected for the delivery of the paper questionnaires, in venues offered by the HPDA (section 5.8.1).

### 5.5.3. Questionnaire length

The researcher attempted to design a relevant short internet questionnaire, completed in less than 30 minutes (Deutskens et al., 2004; Marcus et al., 2007). In determining questionnaire's ideal length, previous studies considered the time it takes an average respondent to complete the questionnaire, rather than the number of questions included. Although some studies concluded that the questionnaire length is not associated with the response rates (Cook et al., 2000; McCambridge et al., 2011); other trials showed that shorter internet based questionnaires (15 to 30 minutes to be completed) may increase response rates than longer versions (Deutskens et al., 2004; Marcus et al., 2007). Lastly, long questionnaires may be responsible for fatigue of respondents and errors arising from inattention, and incomplete answers (Converse and Presser, 1986).

Similarly, shorter versions of paper questionnaires are generally associated with higher response rates and full-completed questionnaires. However, there is no agreement among the studies about the definitions of 'long' and 'short' questionnaires regarding the number of items or paper pages. Short questionnaires may vary between one and six pages, whereas long between two and 36. In addition, the items may differ in complexity (Rattray and Jones, 2007; Rolstad et al., 2011).

#### 5.5.4. Questionnaire's title and instructions

The title was relevant to the questionnaire's context. It was not formulated as question; as it is unsure whether a question-title attracts or repels the respondents (de Leeuw et al., 2008). The instructions for the completion of the questionnaire were as simple as possible. Complex routing instructions may reduce motivation and lead to inaccurate answers or indiscriminate box ticking when there are closed questions (Schaeffer and Dykema, 2011).

#### 5.5.5. Formulation of questions

##### *Selection of items*

A standardised procedure was followed for the selection of items (Boynton and Greenhalgh, 2004). Firstly, validated disease specific instruments for PD and emotional well-being, and relevant literature (articles, books, handbooks for PD published by national and international organisations) were collected and read carefully. Secondly, a draft outline with items grouped into categories was written by the researcher. Thirdly, the selected items were discussed with the supervisory team, and healthcare professionals working in Greece. Although the consultation of patients is an important concept for the construction of a questionnaire in many countries (Bressee, 2014), this is not the case in Greece. Indeed, the HPDA refused the communication of the researcher with its members for the selection of items for the current questionnaire. Instead, the consultation of a neurologist specialised in PD and two physiotherapists with experience in PD, was proposed. Fourthly, based on the recommendations of professionals, the items of the final version were selected (Boynton and Greenhalgh, 2004).

*Order of questions*

The questionnaire followed a "funnel technique" by placing easier questions first, based on the subjective opinion of the principal researcher; and general questions before specific questions (Williams, 2003). This procedure may increase respondents' confidence; and they are less likely to quit the questionnaire, compared with questionnaires that difficult items are placed earlier (Williams, 2003; Holtgraves, 2004). The selected items, were also grouped into themes to facilitate the questionnaire's completion, to increase response rates due to questionnaire's enhanced internal consistency (Lam et al., 2002), and facilitate the analysis section (Anderson, 1998).

Despite the fact that the "funnel technique" supports the placement of the socio-demographic questions at the end of the questionnaire, to avoid negative feelings about the provision of personal information that may impact the answering behaviour or participation (Zikmund and Babin, 2012); in the current questionnaire, socio-demographic items and questions related to PD and health status were placed in section A (Background information). In addition, the patient's name was asked in order to ensure that just one questionnaire was completed for each patient. To avoid respondents' negative reactions, the invitation letter explained the aim of the current survey, and guaranteed the protection of personal information (Boynton et al., 2004).

*Question length*

The question length was kept as short as possible in one sentence, as questions with more than 20 words may be associated with greater comprehension difficulty (Schaeffer and Dykema, 2011). Although it is supported that sensitive questions may include more than one sentence and more words, because short sensitive questions can be perceived as abrupt and threatening (Boynton and Greenhalgh, 2004); in this survey the sensitive questions of the Section A were short, as the invitation letter guaranteed confidentiality and anonymity to persuade respondents to answer all the items.

*Wording and phrasing*

Familiar phrases, everyday terms and words were preferred; which do not have nuances, alternative or even opposite meanings to respondents. Similarly, medical terms were used as little as possible, because their overuse may be a reason for respondents to quit the questionnaire (Bradburn et al., 2004). Grammatical complexities were kept to a minimum, because they may increase the number of blank or socially desirable responses (Boynton et al., 2004). In addition, simple language is a crucial element in senior and less educated population, as these individuals may have greater difficulties with comprehension of survey questions (Holbrook et al., 2006).

Questions were formulated in active rather than passive voice to increase the respondents' comprehension (Bell, 2005; Lietz, 2010). Negatively worded questions were also excluded, because they have been found to take longer to process and there are increased possibilities for respondents to make mistakes (Lietz, 2010). There were also brief explanations for some questions into a parenthesis to ensure that they were understood by the respondents (Mullen and Daniels, 2009).

*Question format*

The survey's questions were formatted mainly for closed-ended responses, with definitive answers. However, few questions of section A and the question at the end of the questionnaire were open-ended, with no fixed answers. Closed questions were preferred, because: they are usually completed in few seconds; they are associated with higher response rates; they facilitate the data analysis, as their answers can be transformed into numerical values (Brace 2013). They may also be more suitable, because many PD patients face writing difficulties. The closed-ended questions of sections B to E were memory questions about motor function and emotional well-being. As the recall of events or behaviours may be difficult to being answered (Bell, 2005), the memory questions of the current project were referred to the immediate past (previous week). Furthermore, only basic ADLs were asked, as this information may have been committed to memory (Jack and Clarke, 1998).



The open-ended question at the end of the survey about 'additional comments', allowed respondents whose feelings and thoughts were aroused by the previous questions, to express themselves in their own way, and provide more information about their experience of being living with PD. Thus, unexpected findings could be detected (O'Cathain and Thomas, 2004).

#### 5.5.6. Formulation of responses

The response options of the closed questions of section A, were categorical, as they were related to the sociodemographic characteristics and health related status of PD patients. The number of response choices varied among the questions in order to exhaust the entire range of answers. As in some questions the range of responses may have been larger than the identified, open-ended items were added (image 5.1, p. 74) (Moule and Goodman, 2009).

The provided possible answers of closed questions in sections B-E were given using a five-point verbal rating scale. More response options were excluded, because when long response scales (at least seven options) are used, the respondents may not be able to distinguish alternatives between the answer options of each question. On the contrary, respondents can more reliably report their subjective states using response scales between five and seven points (Iarossi, 2006). Adverbs were selected as possible responses. As the adverbs are vague quantifiers and might be interpreted differently by the respondents (Bell, 2005); numeric reference points for a specified time period were given for each adverb into a parenthesis (images 5.2, p. 76; and 5.3, p. 79). (Baker, 2003; Bradburn et al., 2004).

It was decided to have a 'leave it blank' option' instead of a 'don't know' response for those who were uncertain for their answer or were not willing to response for personal reasons (Lam et al., 2002). Although there is some controversy in the literature whether providing a 'don't know' option is reasonable, it seems that their absence does not significantly affect

the response rates, compared with 'leave it blank' option (Poe et al., 1988). Additionally, in questionnaires with a 'don't know' option, even some participants who initially are sure about their response, finally they may prefer to choose the 'don't know' option (Gilljam and Granberg, 1993). Lastly, questionnaires with 'leave it blank' option are slightly shorter and are completed in less time (Poe et al., 1988).

<p>What is your primary mean of transportation, except getting around on foot?</p> <p><input type="checkbox"/> personal automobile</p> <p><input type="checkbox"/> friend's, relative's or neighbor's automobile</p> <p><input type="checkbox"/> metro</p> <p><input type="checkbox"/> bus</p> <p><input type="checkbox"/> taxi</p> <p><input type="checkbox"/> other</p> <p>If you have ticked other, please specify: .....</p>
--

**Image 5.1.** Example of a question of Section A (paper-based questionnaire).

#### 5.5.7. Questionnaire's structure

The questionnaire's title was placed on the top of the questionnaire, and below the instructions for its completion (Boynton et al., 2004; Marshall, 2005). The questionnaire was not anonymous in order to ensure that there was just one completed questionnaire for each patient. The questionnaire's items were grouped into five sections, as seen in table 5.2 (p. 75). An opened question for additional comments and a thank-you statement were included at the end (Bradbrum et al., 2004). Section A included socio-demographic items, items related to PD and general health status. The items of sections B to D assessed the restrictions in daily life, due to the motor symptoms of PD. Lastly, section E was related to the emotional well-being.

**Table 5.2.** Sections of questionnaire and number of included items.

Section number	Section title	Number of included items
A	Background information	16
B	Walking	12
C	Transfers and sitting	6
D	Hand activities	8
E	Emotional well-being	9
<b>Total number of items:</b>		<b>51</b>

#### 5.5.8. Questionnaire layout (online questionnaire)

Special attention was given to the questionnaire's visual appearance to attract the potential respondents and facilitate the completion process. The general rule suggesting 'simple in appearance, but sophisticated questionnaires' was followed (Marshall, 2005). The Google Forms, which is a part of the Google Drive suite, was selected for the building of the online questionnaire. It is a free survey tool, suitable for the design of simple questionnaires in academic and research field (Smallwood, 2015). The 'required login' option was not ticked in order to access the questionnaire individuals without a google account (Fan and Yan, 2010). The questionnaire was available at the link:

[http://docs.google.com/forms/d/1JYku5P\\_ItJGvGwVTriSBVCQ0A-HAh0iTptYTive2Rbo/viewform](http://docs.google.com/forms/d/1JYku5P_ItJGvGwVTriSBVCQ0A-HAh0iTptYTive2Rbo/viewform)

The form background was in white colour, and the internet page background in dark cyan. Concerning the text, the questionnaire's title was written in blue colour, the word "required" for the two required questions in red, and the rest text in black. Bold and capital letters were used, similarly to the paper questionnaire. The 'Times New Roman' typeface for the whole survey was selected. In addition, 'extra-large' font size and 'centre align' were ticked for the survey's title; and 'large' font size and 'left align' for the rest parts of the

survey. The asterisk symbol identified the required items for completion (consent form, and if the respondent was a PD patient or carer).

With respect to the design of the sections and items, the numbering was similar to the paper questionnaire (section 5.5.9). Depending on the question's type, the appropriate options were selected. Analytically, these were: 'date' for the questionnaire's completion date, 'multiple choice' for the closed questions, 'text' for the open questions required a short answer, and 'paragraph text' for the open questions required a relative long answer. The Google Forms programme automatically designed the visual appearance of questions and their responses. The appearance of closed questions of sections B to E is presented in image 5.2.

**04.... Had difficulty turning in a forward position?**

- ☐ never (0 days a week)
- ☐ occasionally (1-2 days a week)
- ☐ sometimes (3-4 days a week)
- ☐ often (5-6 days a week)
- ☐ always (7 days a week)

**Image 5.2.** Question B.04 of the online survey.

It was also decided to include multiple items per screen (online page). Although, there are no significant differences in the total completion time between multiple and single items per screen for internet surveys; the number of missed questions is significantly higher in single items per screen (Couper et al., 2001). The contents per screen of the current online questionnaire are presented in table 5.3 (p. 77).

Lastly, buttons and a progress bar were incorporated to help respondents navigate through the questionnaire. The "back" and "continue" button allowed respondents to move

backward and forward within the questionnaire. The voluntary completion of the questions (except the required items on the first page) did not require respondents to answer the questions of each page before moving on to the next one. The progress bar was an easy way to let the respondents know where they were in the questionnaire. At the end of the questionnaire there was the “submit” button for the online submission (Smallwood, 2015).

**Table 5.3.** Contents per screen for the online questionnaire.

Number of screen	Contents
1	Consent form, instructions for the questionnaire’s completion; patient’s name; date
2	Section A (Background information)
3	Section B (Walking)
4	Section C (Transfers and sitting)
5	Section D (Hand activities)
6	Section E (Emotional well-being)
7	Open-ended question for additional comments; thank-you statement

#### 5.5.9. Questionnaire layout (paper questionnaire)

Regarding the paper questionnaire, a booklet format was preferred, which was stapled in two places along the fold in the manner of a magazine, for two reasons. Firstly, it is easier to complete it compared with questionnaires stapled on the corner, and secondly it was longer than four pages (Anderson, 1998). Although, it was printed on both sides of the paper, the booklet format minimises the possibilities of missing the reverse pages (McDonald, 2012). The questionnaire was printed on A4 sheets, as respondents generally find A4 sheets easier to handle than A3 sheets (McColl, 1994), and are associated with higher response rates than smaller sized papers. However, a cover page was not added, as it does not significantly increase the response rate (de Rada, 2005). The questionnaire was printed on white-coloured paper, because it is an acceptable colour for questionnaires. Black ink was used to contrast sufficiently from the white paper, so that the questionnaire could be read easily (Bradburn et al., 2004). Only the logo of the HPDA was allowed to add

on the first page of the questionnaire. It was printed in colour to increase attraction and add prestige (Anderson, 1998).

The 'Times New Roman' typeface was selected; font size 16 for the title of the questionnaire, and 14 for the rest parts of the questionnaire; and 1.15 line spacing. These parameters are recommended for the elderly population, due to visual impairments (Williams, 2003). Bold and capital letters -in some parts- were used to draw attention and ensure emphasis; instead of italics and underlying words or phrases, which make reading more difficult. However, the overuse of capital letters was avoided, and lower cases were preferred, which are easier to read. The numbering of pages (Arabic numbering), sections and items decreased the possibilities of missing a question. The numbering of questions and sections also facilitated the analysis process (Iarossi, 2006).

Regarding the overall design, the questions were put into boxes to be more attractive (Marshall, 2005); and none of the questions were split over two pages, as this may cause confusion (Murray, 1999). With respect to section A, a tick box was placed on the left of the response option to be more attractive; whereas the possible answers were placed in one column (image 5.1, p. 74), to minimise the danger of missing the answers of the second column (Moule and Goodman, 2009). The provided space for the short opened questions or the open ended items of closed questions was a single or two lines (image 5.1, p. 74) (Edwards, 2010). Regarding sections B to E, a matrix table questionnaire was designed (image 5.3, p. 79). This format is a convenient way to collect multiple responses, if the response options are the same and all the questions are under the same topic. (Dillman, 2007). Although there is no strong evidence about the placement of answers (Lietz, 2010), frequency adverbs of lower numerical values were placed on the left. Lastly, a big box was used for the response of the last open question. Lines are not recommended in relatively long answers, as they make the questionnaires look more crowded and have not any useful function (Edwards, 2010). The Greek and English version of the paper questionnaire are in supplements 1 and 2 respectively.

Due to Parkinson's disease, how often during the last week have you....		Never (0 days a week)	Occasionally (1-2 days a week)	Sometimes (3-4 days a week)	Often (5-6 days a week)	Always (7 days a week)
01	Had difficulty taking the first step when you begin walking?					
02	Taken smaller steps when walking, which get faster as you walk?					

**Image 5.3.** Matrix table questionnaire (paper-based questionnaire).

#### 5.5.10. Translation of the questionnaire

A special characteristic of this survey was that the PhD studies were taken place in the United Kingdom; whereas the research was conducted in Greece. Firstly, the questionnaire was designed in Greek with the assistance of healthcare professionals working in Greece (section 5.5.5). Greek was the native language of the researcher and the language of the target population. However, the questionnaire had to be translated in English in order to be presented to the supervisory team of the University. As the original version of the questionnaire was written in the language of the target population; the steps recommended by the World Health Organisation (WHO) to achieve different language versions of the English instrument, were not followed (Behling and Law, 2000). Instead an official translator, with previous experience in the translation of healthcare documents, was sought for the translation of the questionnaire from Greek to English, in order to avoid errors in conceptual translation. It should be pointed out that the Greek version of the questionnaire was written in demotic (δημοτική) Greek, a form of Greek language spoken in everyday life in Greece; and is understandable by all the Greeks, irrespective of their local dialect.

## **5.6. Ethical consideration**

### 5.6.1. Ethical approval

Ethical approval for the entire study was granted by the Manchester Metropolitan University Research Ethics Committee; and the Scientific Committee of the HPDA “Epikouros-kinisi” on 25<sup>th</sup> May 2011, protocol number 12/2011 (Appendices 5.1 and 5.2). An additional ethical approval for the survey was obtained from the HPDA on 1<sup>st</sup> October 2013 (appendix 5.3).

### 5.6.2. Informed consent

The subjects were informed about the true nature of the survey (Boynton et al., 2013). The goals of the survey and the components of the study’s procedure were conveyed in their totality to the respondents through the invitation e-mail for the online survey (Appendices 5.4-5.5), and the invitation sheets for the paper survey (Appendices 5.6-5.7).

Although a signed consent form is not generally required for survey studies; it was decided to include a consent form, as the questionnaire was not anonymous (Iarossi, 2006). Consent was obtained voluntarily, without pressure, inducements or influence. The consent form indicated that the respondents had understood all the information relevant to the study nature and its purpose (Moule and Goodman, 2009). In the paper survey, there was a space to sign at the bottom of the information sheet (Appendices 5.6 and 5.7). In the online survey the respondents had to tick the ‘I agree’ option, which was a required field, before the completion of the online questionnaire (image 5.4, p. 81). An electronic signature was not asked, as the respondents may have not been familiar with it. Lastly, no incentives were promised to them for their participation.



<p>Consent form for the questionnaire</p> <p>Before the completion of the questionnaire, be sure that you have read the invitation e-mail sent to you; and tick the follow box, if you agree to participate in the study.</p> <p><input type="radio"/> I accept</p>
---

**Image 5.4.** Consent form for the online survey.

### 5.6.3. Confidentiality

Confidentiality was kept at all times. Data gathered on paper were kept on a locked cabinet in researcher's house. All paper data were not moved outside the researcher's house. An access password, known only to the researcher, protected the information stored on a computer. The backup external memory of electronic data was also password protected, and locked into the cabinet. No one had access to the online questionnaires beyond two members of the research team (psychologist, nurse) and the president of the HPDA. The completed paper questionnaires were put into closed envelopes by the respondents, before returning back to researcher. Participants' records were only seen or discussed only by authorised personnel relevant to the study, after the permission of the researcher. Confidentiality was also kept by presenting statistical tabulations by broad enough categories, so that individual respondents could not be singled out. Finally, at the end of the study, all data gathered on paper were destroyed using a paper shredder; whereas all data kept on the computer and external memory were deleted from the recycle bin of the computer.

### 5.6.5. Anonymity

Participants' names remained anonymous during and after the completion of the study. The names did not appear in any documentation. Each participant had a special code and the name in the questionnaire was replaced by this code. The same code was also used for the data analysis. The participants were not identified by name or other defining characteristics at any point in the study. Instead of the name, the personal code was used for each participant. In addition, it was prohibited to the members of the research team to

give the respondents' names and the completed paper-based questionnaires to anyone outside the research team and the president of the HPDA.

#### 5.6.6. Harm

There was no risk for harm, due to the study's nature (survey). In addition, the answering of any item on the questionnaire was voluntary; and there were not unethical questions.

#### 5.6.7. Rights of participants

The participants had the right to quit the study before submitting the questionnaire. They could also being informed about the results of the study, if they wished.

### **5.7. Pretesting and pilot work**

Before the main survey, a pretesting was performed for the online survey, and a pilot work for both the online and paper questionnaire. The pretesting was performed on 17<sup>th</sup> August 2013; the pilot work for the online questionnaire between 20<sup>th</sup> August and 20<sup>th</sup> September 2013, and the pilot work for the paper survey on 18<sup>th</sup> November 2013.

#### 5.7.1. Pretesting (online questionnaire)

Pretesting is an unofficial, unscientific and very simple way to find errors before delivering the self-administrated questionnaires for the pilot work (Holdbrook, 2006). Once the supervisory team of the University agreed that the questionnaire could be delivered to the target population; four adults, free of PD, accessed the online Greek version to check the spelling, grammar and layout, and complete the questionnaire (Boynton, 2004). Their feedback was positive, no changes were proposed, and the questionnaire was delivered for the pilot work.

### 5.7.2. Pilot work (online questionnaire)

#### *Aim and objectives*

The general aim of the pilot work - both for the online and paper questionnaire- was to test the questionnaire as a whole under real survey conditions, before the main study (de Leeuw et al., 2008).

The objectives of the current pilot work were listed as follows:

- To get informed about the estimated response rate of the questionnaires, and the time of questionnaire's completion (de Leeuw et al., 2008).
- To determine whether it was necessary to remove some items or any flaws, which had caused confusion to respondents or led to high number of non-response answers (Marshall, 2005).
- To determine whether additional items, relevant to the study's aim, would be added (Presser et al., 2004).
- To determine whether the questionnaire's layout was suitable for the target population, and the questionnaire easy to complete it.
- To collect information on how respondents may answer in general and specific questions (Boynton, 2004).
- To develop pre-codes for open-ended questions (de Leeuw et al., 2008).
- To check or analyse whether the data produce usable results (Marshall, 2005).

#### *Implementation of the pilot work*

The whole procedure was similar to the main survey (Marshall, 2005). The volunteer (psychologist) sent the questionnaire randomly to 30 individuals, members of the HPDA. This ensured that the respondents were representatives of the study's sample, with similar socio-demographic characteristics (Marshall, 2005). However, there were some differences between the pilot work and the main study, which are listed below:

- At the end of the online survey, there was a 'feedback questionnaire' (Appendix 5.8) with items relevant to the aims of the pilot work. The items' completion was voluntary and there was a 'leave it blank' option.
- The invitation e-mail included additional information about the 'feedback questionnaire'.
- The required time to complete the questionnaire was not reported in the invitation e-mail, as the completion time would be based on the results of the pilot-work.

### *Results*

Due to limitation of time and small number of respondents, the data produced by the pilot were not analysed using the Statistical Package for the Social Sciences (SPSS), or content analysis, as the main survey. However, in order to produce usable results, the answers were checked using the 'summary of responses' and 'view responses' options of the Google Forms.

Eight individuals –five men and three women- submitted the pre-final version of the questionnaire by 19<sup>th</sup> September 2013. Thus, the response rate was 26.67%. Six of the respondents (75%) were PD patients, whereas the others were carers of PD patients. The age -in years- varied from 50 to 81 years, and the disease duration from one to 17 years. Each subject answered at least 76% of the items. All the open-ended questions of the section A were answered clearly. In total, the number of the non-response questions varied from zero to two (up to 33.3%), and it was similar among the survey's sections. However, the open question at the end of the questionnaire, was answered by only two persons.

The respondents' feedback was positive and the overall survey's mark was 8.8 out of ten. The completion time varied from four to 20 minutes. The instructions were understandable, there was no objection to answer any sensitive question, and the online survey was well-designed and easy to complete it. All questions and response options were considered appropriate and comprehensible by seven subjects.

Six individuals reported some activities, which were affected due to PD, and were not included in the questionnaire: swimming (n= 1), sexual disturbances (n= 1), face shaving (n= 1), dysphagia (n= 2), constipation (n= 2), hypotension (n= 1), speech disturbances (n= 1). However, five answers were not related to the motor function or emotional status, and were considered not relevant to the objectives of the current study. It was decided not to add 'swimming' and 'face shaving' to the final version of the questionnaire; because the main study was not conducted during the summer period, and face shaving is related just to males.

#### *Modifications for the main survey*

The pre-final version of the questionnaire was not subjected to any modifications, and it was considered the final version of the questionnaire. In addition, the final version of the e-mail invitation included the estimated time of completion, based on the answers of the pilot work. Lastly, the number of individuals, in which the online invitation would sent, recalculated; due to the lower response rate (26.67%) than those reported in the literature (34%) (Shih and Fan, 2008). Hence, the invitation had to be sent to at least 1440 subjects, instead of 1130 (section 5.4.2).

#### 5.7.3. Pilot work (paper questionnaire)

Two PD patients completed the paper questionnaire at the neurological medical office of the president of the HPDA. As the online pre-final version piloted successfully, it was decided not to include further respondents for the current pilot work. The implementation of the pilot work did not differ from the procedure followed in the main study. No reconstructions were made to the final version of the questionnaire, as the participants' feedback was positive.

### **5.8. Implementation of the main survey**

#### 5.8.1. Location and study's calendar

After the questionnaire was piloted, it was administrated to the target population (Murray, 1999). The delivery, completion and collection of questionnaires were conducted from October 2013 to May 2014. Specifically, the online questionnaires were completed from

2<sup>nd</sup> October 2013 to 12<sup>th</sup> February 2014, whereas the paper questionnaires from 21<sup>st</sup> November 2013 to 22<sup>nd</sup> May 2014.

The paper survey was conducted at the offices of Parkinson Care (address: 121 Spetson Street, Kypseli, 113 63, Athens), on Mondays and Thursdays from 16:00 to 20:00; and the neurological medical office of the president of the HPDA (address: 127 Galatsiou Avenue, Galatsi, 111 46, Athens), on Fridays from 14:30 to 16:30, during the operating days and hours for PD patients-members of the HPDA. These facilities are offered free to the HPDA, the aforementioned days and hours, to provide free services to its members.

#### 5.8.2. Online survey

The first step of the online survey was to send an invitation e-mail (Appendices 5.4 and 5.5) to the target population. The aim of the invitation was to gain the respondents' cooperation, and feel confident to answer the questions and express their views openly. In addition, the surveys that include invitation letter are associated with increased response rates (Iarossi, 2006; Bernd et al., 2007). The recalculation of the target population to which the invitation had to be sent, following the pilot work, exceeded the total number of individuals enrolled with the HPDA. Thus, it was decided to send the online invitation to all the members of the HPDA, except those whom the invitation for the pilot study was sent. It was also decided that the invitation e-mails would be sent, based on the way that the members of the HPDA appear on the organisation's list; that is, according to the chronological order of enrolment with the organisation, from the newest to the oldest. As the principal researcher was not allowed to have access to the database with all the personal information of the members of the HPDA; one volunteer (psychologist), who had access to the database, sent the online invitations. The time of the survey's conduction, the HPDA did not have a newsletter service. Hence, the invitations had to be sent to each member separately. The official e-mail of the HPDA was used, to avoid spam issues, and for prestige. In addition, the internet users may be distrustful to click on a provided link, when no previous relation with the sender exists (de Leeuw et al., 2008). Based on the volunteer's availability, it was decided to send 200 online invitations per month, except holiday periods (e.g. Christmas) to avoid higher non response rates (Iarossi, 2006). The principal researcher

had immediate access to the completed questionnaires. Thus, he was able to check the answers and be aware of the response rates.

In the meanwhile an announcement relevant to the study, without including the survey's link, was posted on the official webpage (<http://www.parkinsonportal.gr/epikouros.php>) and facebook page (<https://www.facebook.com/Parkinson.EPIKOYROS.kinesis/?fref=ts>) of the HPDA. The aim of the announcement was to inform members of the HPDA, who did not check their e-mails.

Two reminder (follow-up) e-mails were sent to the potential respondents to get informed about deadline of submission and the uniform resource locator (URL) to access the questionnaire, in order to maximise the response rates. No further reminder e-mails were sent, as there is evidence that they do not increase the response rates, and repeated follow-ups may be considered as spam (Bell, 2005; Iarossi, 2006). The volunteer sent the reminder e-mails to the whole sample, because the Google Form does not provide to the researchers the e-mail address of respondents (Marshall, 2005). As there is not a general rule about the time of sending the reminder e-mails (Deutskens et al., 2004), and based on the average response rates for the online surveys (5.59 days) (Ilieva et al., 2002); it was decided to send the first and second reminder one and three weeks respectively after the date the invitation e-mail was sent. The same dates, a reminder announcement on the official website and facebook page of the HPDA was posted.

The first 200 invitation e-mails were sent from 2<sup>nd</sup> to 4<sup>th</sup> October 2013. However, there was one failure e-mail (invalid e-mail address). Despite the follow-up e-mails, the response rate was very low (14.5%); lower than the pilot work (26.67%). In addition the availability of the volunteer was limited for the next months. As hence, on 10<sup>th</sup> November, it was decided to stop the online survey, and conduct a paper survey as an alternative. The flowchart with the number of respondents for the online survey is seen in figure 6.1 (p. 94).

### 5.8.3. Paper survey

The members of the HPDA were informed about the paper survey through monthly announcements on the official webpage and the Facebook page of the HPDA, and through direct contact of principal researcher or volunteer (nurse) with PD patients or their carers. The contact through e-mail was rejected, because it was proved ineffective for the online survey.

The survey was conducted with personal delivery of questionnaires to PD patients or their caregivers. Firstly, the purpose of the study was explained briefly, and the information sheet (Appendices 5.6 and 5.7) was given to those expressed interest to participate. After reading it, they were asked to sign the consent form (Appendices 5.6 and 5.7), if they were willing to complete the questionnaire; and the paper questionnaire, inside an opened envelope, and a pen were given to them. Furthermore, any question related to the study was answered. The link for the online survey (printed online invitation) was given to respondents that were willing to participate in the study, but were unable to complete the paper questionnaire that time. However, only one individual completed the online survey since 21<sup>st</sup> November 2013.

The rooms were equipped with a table and a chair to complete the self-administrated questionnaire. The furniture was placed in a quiet corner of the room, away from other people; to eliminate bias arising from lack of privacy, and interaction of being in the same place with other individuals (Boynton et al., 2004). In case of inability a PD patient to complete the questionnaire, a person who accompanied him/her could provide assistance. In case of an absence of a person accompanied the patient, the principal researcher or nurse did not assist the respondent to complete the survey, to avoid interviewer bias (Bell, 2005).

Two to three minutes after the start of questionnaire's completion, the respondent was asked if everything was understood, and whether the required item on the first page had been completed. Further guidance was provided, if needed, during the whole completion of the questionnaire. The researcher was careful while giving explanations; to avoid:



inflections of the voice, facial expressions and gestures, as they may influence responses (Boynton et al., 2004). The completed questionnaires were returned back to the researcher into a sealed envelope, to protect the privacy of their answers from other persons being in the same room (Iarossi, 2006); and was thanked for the participation.

The procedure for the collection of completed questionnaires was relatively slow. On 22<sup>nd</sup> May 2014, after receiving 200 completed online and paper surveys, it was decided to stop the study and proceed to the analysis. 197 individuals were asked to complete the paper survey; however, 27 refused. Although, they were not asked about the reason(s) for refusal; some claimed restriction of time or *“the study has nothing to offer to me”*. The flowchart with the number of respondents for the paper survey is seen in figure 6.2 (p. 96).

### **5.9. Data analysis**

Before the data analysis, the coding of survey questionnaires was performed. Each questionnaire had a unique serial number, which was a combination of upper-case letters and numbers (e.g. O21, P148). The letter ‘O’ was selected for the online questionnaires and ‘P’ for the paper questionnaires.

Only completed questionnaires were included in the analysis; whereas uncompleted questionnaires were excluded. A questionnaire was considered completed if at least the half items of the whole questionnaire, and one item from each section had been answered; as this may provide the most important information for the patient (Iarossi, 2006). Both quantitative (descriptive statistics) and qualitative techniques were selected for the analysis and interpretation of data, based on the research aim and objectives (Sections 5.2.1 and 5.2.3).

### 5.9.1. Quantitative analysis

The responses of closed questions of sections A-E, and the short open-ended questions of section A were transformed into quantitative data. The data were entered to the 'Variable View' of SPSS, and all the variables were defined (named and coded) (Pallant, 2016). Their analysis was performed using the SPSS version 22.0. The level of statistical significance (alpha level) was set at  $\alpha < .05$ . (Sim and Wright, 2000; Hicks, 2009). With respect to the missing data of the questionnaire, it was decided to not being replaced with the mean. This option is not recommended, as it can severely distort the results of the analysis (Pallant, 2016).

Two types of analysis were performed: one for the whole sample, and one sub-group analysis between males and females (only for the items of Section A). The aim of analysis for the whole sample was to detect: the socio-demographic characteristics of PD population, their health-related status, and the most frequent mobility and emotional disturbances. Thus, descriptive statistics were obtained for the categorical and continuous variables of the questionnaire. 'Summary' statistics; such as minimum, maximum, range, mean, median and standard deviation (SD) were provided for the continuous variables; whereas number of answers and proportions for the categorical variables (Hicks, 2009; Pallant, 2016). The aim of subgroup analysis was to identify any significant difference between males and females with respect to their socio-demographic characteristics and health status (Section A). For this purpose Chi-square tests for independence were applied to explore the relationship between two categorical variables (Hicks, 2009; Pallant, 2016).

### 5.9.2. Qualitative analysis

The comments of respondents at the end of the questionnaire and few items of section A were analysed using qualitative analysis. Among the several analysis methods in qualitative research, the thematic analysis -a form of content analysis- was selected; because it is defined as a systematic approach to categorise data for the purpose of classification, summarisation and tabulation. It is also a qualitative descriptive approach, suitable for researchers who wish to employ a relatively low level of interpretation; describing a

phenomenon in a conceptual form. In addition, by using content analysis, it is possible to analyse data qualitatively, and at the same time quantify the data. Moreover, thematic analysis is recommended when the approach is inductive<sup>11</sup> (Krippendorff, 2013; Vaismoradi et al., 2013). Thus, the thematic analysis would assist the researcher to create themes, summarise and categorise the beliefs of respondents about their experiences living with PD.

In the current study, an official translator was consulted for the conceptual translation of some phrases from the Greek to the English language. The material was analysed in its entirety. A manifest analysis was followed, as the analysis focused on what was actually written by the respondents, rather than what the researcher believed (Bengtsson, 2016).

The process of data analysis according to Elo and Kyngäs (2008) was followed. Firstly, during the “preparation” phase, the responses were read several times to get familiarised and the initial ideas for the categorisation of data were noted down. Secondly, during the “organising” phase, based on the available data, categories and subcategories were identified. The themes were checked carefully to avoid any overlap. Words and phrases of the categories were coded and counted (quantitative content analysis). However, some statements of interest, based on the researcher’s view, were presented in words (qualitative analysis); to provide further information to the readers. In addition, the irrelevant data were deleted. This process was performed with caution to avoid the losing of important information for the analysis. Finally, in the third step the results were reported, as seen in section 6.3.

To increase validity, Investigator triangulation was followed; involving two investigators that performed the analysis separately: the PhD student and a Greek physiotherapist with previous experience in qualitative analysis. Then, their results were compared; disagreements, regarding the categories and subcategories, were solved by discussion; and

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<sup>11</sup> No hypothesis is tested

the more appropriate way for the presentation of the results was decided (Bengtsson, 2016).

#### **5.10. Summary of Chapter 5**

- A mixed mode survey, including an online and a paper questionnaire, was conducted to detect the restrictions in ADLs and emotional disturbances among Greek population suffering from PD.
- The most prevalent answers would be considered for the design of the group exercise and education programme of the current thesis (RCT).
- The respondents could be either patients with PD or carers of persons with PD.
- The design of the questionnaire aimed to achieve increased response rates, receive accurate responses, and facilitate its completion and analysis.
- Before the main survey, a pretesting and a pilot work were conducted to identify any errors.
- Although, based on the sample size determination, the required sample had to be 384 individuals; the study stopped when 200 questionnaires were received, due to low response rates and slow process.
- Both quantitative and qualitative techniques were used for the data analysis, as the questionnaire consisted of both close-ended and open-ended questions.
- Only completed questionnaires were included in the analysis. A questionnaire was considered completed if at least the half items of the whole questionnaire, and one item from each section had been answered.

# **CHAPTER 6**

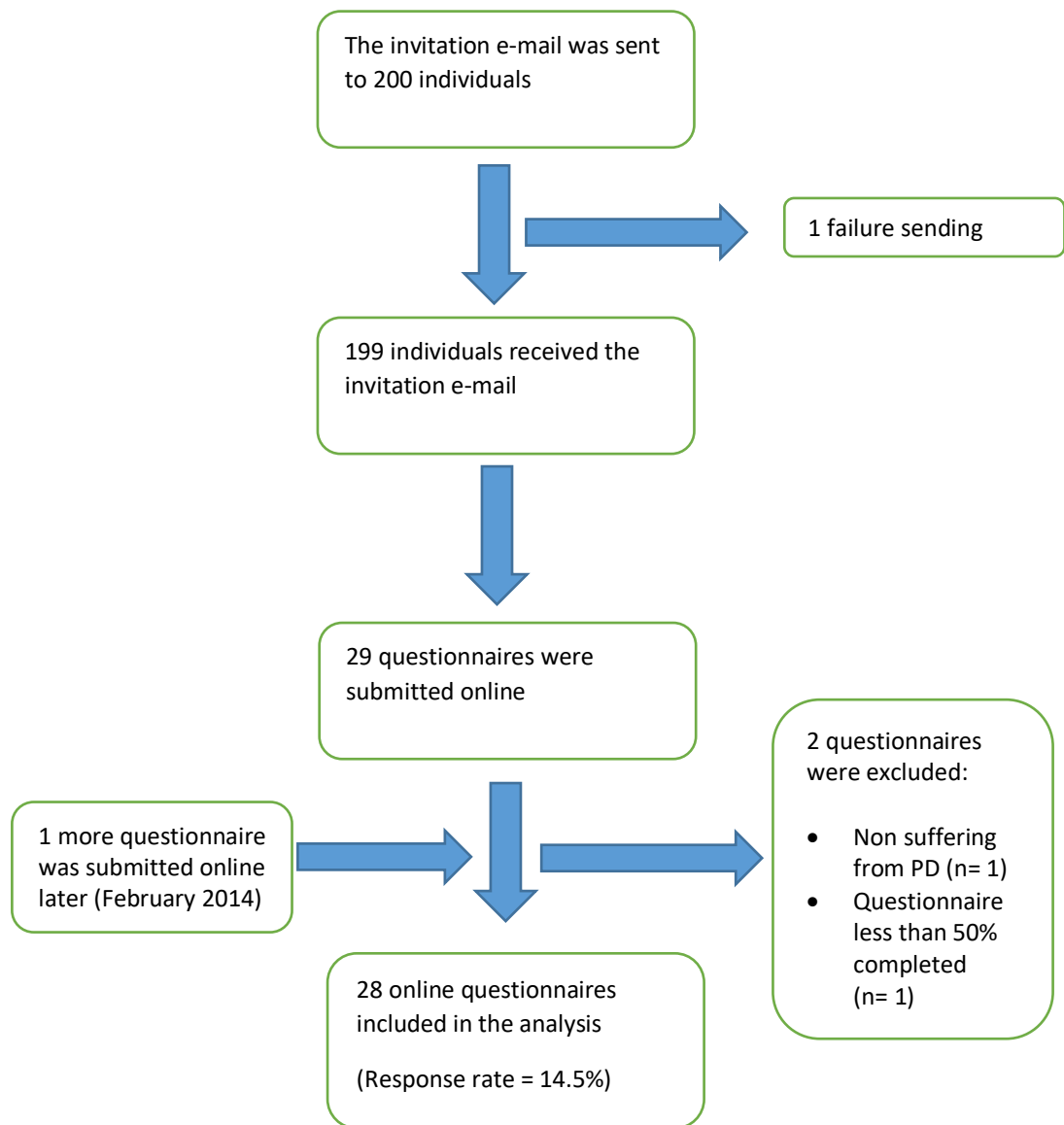
## **SURVEY - RESULTS**

### **6.1. Introduction**

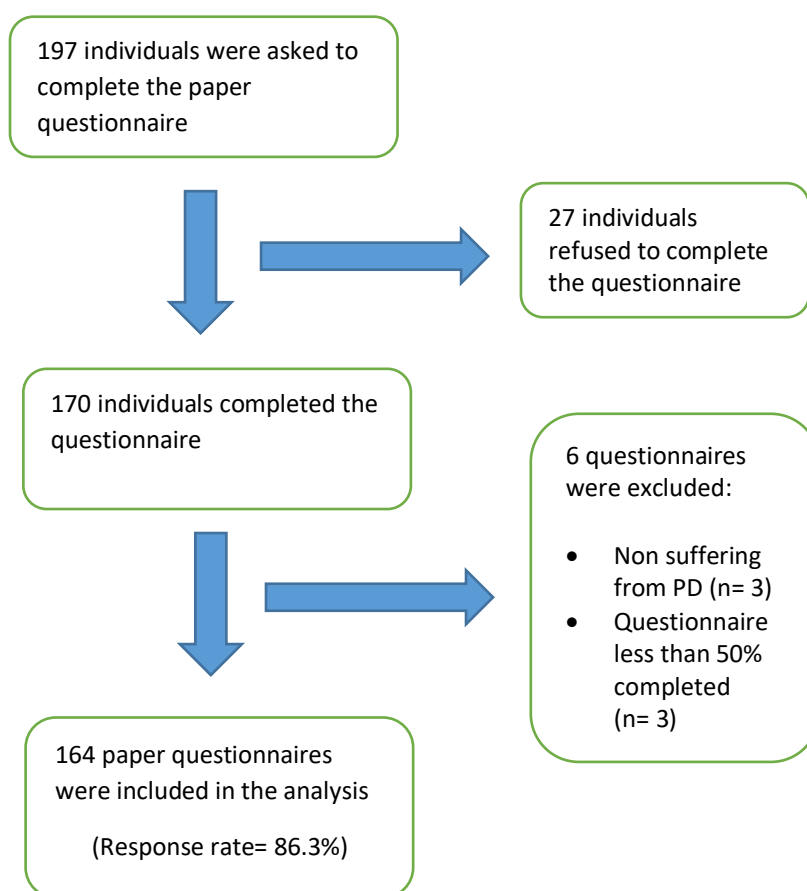
The current Chapter refers to the combined results for the online and paper survey. The Chapter is divided into two main parts: the findings of Sections A-E, where quantitative approaches were applied; and the findings of the last open-ended question, where qualitative analysis was performed.

### **6.2. Number of respondents**

Overall 200 questionnaires were collected (30 online and 170 paper questionnaires), whereas 192 were considered completed and included in the analysis section (28 online and 164 paper-based). The check of patients' names revealed that just one questionnaire was completed for each patient. The flowchart with the number of respondents for the online survey is seen in figure 6.1 (p. 95), whereas the flowchart for the paper survey in figure 6.2 (p. 96).



**Figure 6.1.** Flowchart of the number of respondents for the online survey.



**Figure 6.2.** Flowchart of the number of respondents for the paper survey.

### 6.3. Part one: quantitative results

#### 6.3.1. Section A

##### *Socio-demographic characteristics*

The socio-demographic characteristics of PD patients for the whole population, and for males and females; are presented in table 6.1 (p. 98). As seen in the table, the number of questionnaires completed by PD patients (n= 97) and carers (n= 95) was almost equal. Although the reasons that almost half questionnaires were completed by carers of persons



with PD was not explored; it is believed that writing difficulties due to the disease, cognitive impairments, inability to read and write, and low level of computer literacy may have prevented patients to complete either the online or paper survey.

The findings indicated that the PD patients were almost Greeks (96.9%). All the participants were able to speak Greek; however, five reported Greek as not their native language. Males (55.2%) were more than females (44.8%). Despite the fact that the mean age of patients was 68.31 years, and the retirement age in Greece when the survey was conducted was 65 years; only 13.6% of patients were currently working, either in the public (n= 10) or in the private (n= 16) domain. Seven people reported the reason that were unable to work: six of them due to problems arising from PD; and one due to mobility restrictions related to aging. A further analysis showed that 18 individuals up to 64 years were retired, whereas only two individuals more than 65 years were still working.

Regarding the place of residence, the respondents were counted based on their administrative and regional units (Section 2.4). The majority were from the mainland (n= 172, 91.5%), and only 16 (8.5%) were islanders. The survey population was from 26 regional units and from 11 administrative units. The vast majority (68.2%) was living in Attica (Athens Metropolitan Area). Specifically, the three most reported regional units were: Attica (n= 131); Thessaloniki (n= 8) and Euboea (n= 7). In addition, the distribution of survey population in administrative units was listed as: Attica (n= 131), Central Greece (n= 13), Peloponnese (n= 12), Central Macedonia (n= 10), Western Greece (n= 7), South Aegean (n= 5), North Aegean (n= 3), Epirus (n= 3), Thessaly (n= 2), Eastern Macedonia-Thrace (n= 1), and Crete (n= 1). On the contrary, there were no respondents from Western Macedonia and Ionian Islands.

The primary mean of transportation was car (76.6%). However, as the RCT was decided to hold in Athens; it seems important to report the primary means of transportation for the Athenians, which were listed as follows: car (n= 96, 73.3%), metro (n= 17, 13%), bus 12 (n= 12, 9.2%), taxi (n= 5, 3.8%), and tram (n= 1, 0.8%).

**Table 6.1.** Socio-demographic characteristics for the whole sample, males and females.

Variables		All (n= 192 )	Male (n= 106 )	Female (n= 86)	P value
Survey respondents	PD patient	97 (50.5 %)	51 (48.1 %)	46 (53.5 %)	p = .551 $\chi^2 = 3.55$
	PD caregiver	95 (49.5 %)	55 (51.9 %)	40 (46.5 %)	
Age category (in years)	40-49	8 (4.2 %)	7 (6.6 %)	1 (1.2 %)	p = .416 $\chi^2 = 3.92$
	50-59	37 (19.3 %)	21 (19.8 %)	16 (18.6 %)	
	60-69	50 (24.5 %)	26 (27.9 %)	24 (26 %)	
	70-79	69 (35.9 %)	38 (35.8 %)	31 (36 %)	
	80+	28 (14.6 %)	14 (13.2 %)	14 (16.3 %)	
Nationality	Greek	186 (96.9 %)	102 (96.2 %)	84 (97.6 %)	p = .876 $\chi^2 = .02$
	Greek-Cypriot	1 (0.5 %)	1 (0.9 %)	0 (0 %)	
	Albanian	2 (1.1 %)	1 (0.9 %)	1 (1.2 %)	
	Russian	1 (0.5 %)	1 (0.9 %)	0 (0 %)	
	Ukrainian	1 (0.5 %)	0 (0 %)	1 (1.2 %)	
	Nigerian	1 (0.5 %)	1 (0.9 %)	0 (0 %)	
Native language	Greek	187 (97.4 %)	103 (97.2 %)	84 (97.6 %)	p = .827 $\chi^2 = .04$
	Albanian	2 (1 %)	1 (0.9 %)	1 (1.1 %)	
	Russian	1 (0.5 %)	1 (0.9 %)	0 (0 %)	
	Ukrainian	1 (0.5 %)	0 (0 %)	1 (1.1 %)	
	Igbo	1 (0.5 %)	1 (0.9 %)	0 (0 %)	
Educational level	Primary	48 (25 %)	23 (21.7 %)	25 (29.1 %)	p = .049 $\chi^2 = 7.84$
	Secondary	77 (40.1 %)	41 (38.7 %)	36 (41.9 %)	
	Tertiary*	65 (33.8 %)	41 (38.7 %)	24 (27.9 %)	
	No school	0 (0 %)	0 (0 %)	0 (0 %)	
	N/A	2 (1 %)	1 (0.9 %)	1 (1.1 %)	
Employment status	Employed for wages	17 (8.9 %)	11 (10.4 %)	6 (7 %)	p = .000 $\chi^2 = 26.21$
	Self-employed	9 (4.7 %)	7 (6.7 %)	2 (2.3 %)	
	Retired	127 (66.1 %)	79 (74.5 %)	48 (55.8 %)	
	Household	21 (10.9 %)	2 (1.9 %)	19 (22.1 %)	
	Out of work and looking for work	4 (2.1 %)	1 (0.9 %)	3 (3.5 %)	
	Out of work but not looking for work	7 (3.6 %)	2 (1.9 %)	5 (5.8 %)	
	Unable to work	4 (2.1 %)	2 (1.9 %)	2 (2.3 %)	
	N/A	3 (1.6 %)	2 (1.9 %)	1 (1.1 %)	
Marital status	Married	117 (60.9 %)	69 (65.1 %)	48 (55.8 %)	p = .004 $\chi^2 = 15.58$
	Separated	25 (13 %)	15 (14.2 %)	10 (11.6 %)	
	Widowed	34 (17.7 %)	10 (9.4 %)	24 (27.9 %)	
	Single	11 (5.7 %)	9 (8.5 %)	2 (2.3 %)	
	In a relationship	2 (1 %)	0 (0 %)	2 (2.3 %)	
	N/A	3 (1.6 %)	3 (2.8 %)	0 (0 %)	
Residence	City	150 (78.1 %)	82 (77.4 %)	68 (79.1 %)	p = .989 $\chi^2 = .000$
	Village	39 (20.3 %)	22 (20.8 %)	17 (19.8 %)	
	N/A	3 (1.6 %)	2 (1.8 %)	1 (1.1 %)	
Prefecture	Attiki	131 (68.2 %)	72 (67.9 %)	59 (68.6 %)	p = .155 $\chi^2 = 3.72$
	Thessaloniki	8 (4.2 %)	7 (6.6 %)	1 (1.1 %)	
	Other	49 (25.5 %)	25 (23.6 %)	24 (27.9 %)	
	N/A	4 (2.1 %)	2 (1.9 %)	2 (2.3 %)	
Primary mean of transportation	Car	147 (76.6 %)	83 (78.3 %)	64 (74.4 %)	p = .635 $\chi^2 = 2.55$
	Metro	17 (8.9 %)	8 (7.5 %)	9 (10.5 %)	
	Bus	21 (10.9 %)	12 (11.3 %)	9 (10.5 %)	
	Taxi	6 (3.1 %)	2 (1.9 %)	4 (4.7 %)	
	Tram	1 (0.5 %)	1 (0.9 %)	0 (0 %)	

\* University, College, higher technical school.

Abbreviations. n: number of respondents; N/A: no answer; PD: Parkinson's disease

### Health status

The results of patients' health status are summarised in table 6.2. The median duration of PD (since PD diagnosis) was four years. Almost all the patients (97.2%) were under antiparkinsonian pharmacological treatment. The reason(s) that 2.3% of patients were not receiving treatment, was not investigated. Despite the antiparkinsonian medication, only 28.7% of patients reported significant improvement on PD symptoms. In addition, 92.7% of respondents reported at least one additional comorbidity or previous surgery, classified in six categories. The most common reported comorbidities of each category are presented in table 6.3 (p. 100). Regarding previous surgeries, only four patients reported deep brain stimulation (DBS) due to PD.

**Table 6.2.** Health status for the whole sample, males and females.

Variables		All (n= 192 )	Male (n= 106 )	Female (n= 86)	P value
Years since PD diagnosis	0-11 months	24 (12.5 %)	11 (10.4 %)	13 (15.1 %)	p = .763 $\chi^2 = 1.85$
	1-4 years	76 (39.6 %)	43 (40.6 %)	33 (38.4 %)	
	5-9 years	54 (28.1 %)	32 (30.2 %)	22 (25.6 %)	
	10-19 years	33 (17.2%)	16 (15.1 %)	17 (20 %)	
	20+ years	2 (1 %)	1 (0.9 %)	1 (1.2 %)	
	N/A	3 (1.6 %)	3 (2.8 %)	0 (0 %)	
PD medication	Yes	188 (97.9 %)	104 (98.1 %)	84 (97.7 %)	p = .919 $\chi^2 = .01$
	No	2 (1 %)	0 (0 %)	1 (1.1 %)	
	N/A	2 (1 %)	2 (1.9 %)	1 (1.1 %)	
Improvement of symptoms due to PD medication *	Significant	54 (28.7%)	35 (33.7%)	19 (22.6%)	p = .527 $\chi^2 = 4.16$
	Moderate	48 (25.5 %)	23 (22.1 %)	25 (29.8 %)	
	Little	67 (35.7%)	38 (36.5%)	29 (34.6%)	
	No improvement	16 (8.5 %)	7 (6.7 %)	9 (10.7 %)	
	N/A	3 (1.6 %)	1 (0.9 %)	2 (2.4 %)	
Additional medical conditions /diseases	Yes	178 (92.7 %)	96 (90.6 %)	82 (95.3 %)	p = 1.00 $\chi^2 = .00$
	No	7 (3.6 %)	4 (3.8 %)	3 (3.5 %)	
	N/A	7 (3.6 %)	6 (5.7 %)	1 (1.1 %)	
Sub-categories of comorbidities* **	Cardiovascular disease	68 (38.2 %)	43 (44.8 %)	25 (30.5 %)	
	Respiratory disease	7 (3.9 %)	5 (5.2 %)	2 (2.4 %)	
	Musculoskeletal disease	104 (58.4 %)	61 (63.5 %)	43 (52.4 %)	
	Other neurological disease	4 (2.2 %)	1 (1 %)	3 (3.7 %)	
	Other chronic disease	101 (52.6 %)	56 (58.3 %)	45 (54.9 %)	
	Previous surgeries	148 (83.1 %)	77 (80 %)	71 (86.6 %)	

\* completed only by the respondents who answered 'yes' to the previous question

\*\*some patients reported comorbidities of two or more categories

Abbreviations. n: number of respondents; N/A: no answer; PD: Parkinson's disease.

**Table 6.3.** Most common reported comorbidities for the whole sample.

Sub-categories of comorbidities	Most common comorbidities
Cardiovascular conditions	<ul style="list-style-type: none"> <li>• hypertension (n= 47)</li> <li>• cardiac arrhythmia (n= 11)</li> <li>• coronary artery disease (n= 7).</li> </ul>
Respiratory conditions	<ul style="list-style-type: none"> <li>• chronic obstructive pulmonary disease (n= 4)</li> <li>• bronchial asthma (n= 2)</li> <li>• sleep apnoea (n= 1).</li> </ul>
Musculoskeletal and rheumatoid conditions	<ul style="list-style-type: none"> <li>• low back pain (n= 42)</li> <li>• osteoporosis (n= 31)</li> <li>• osteoarthritis (n= 25)</li> <li>• pain in specific body areas (n= 14) (no information about any specific medical diagnosis)</li> </ul>
Neurological conditions	<ul style="list-style-type: none"> <li>• stroke (n= 2)</li> <li>• dementia (n= 2)</li> </ul>
Other medical conditions	<ul style="list-style-type: none"> <li>• high levels of low density lipoprotein (n= 38)</li> <li>• diabetes mellitus type II (n= 16)</li> <li>• hypothyroidism (n= 9).</li> </ul>
Previous surgeries	<ul style="list-style-type: none"> <li>• hernia surgery (n= 16)</li> <li>• joint replacement (n= 12)</li> <li>• hysterectomy (n= 10)</li> </ul>

Abbreviations. n: number of respondents.

### *Gender differences*

As seen in table 6.1 (p. 98) and 6.2 (p. 99) significant gender differences were reported only for some socio-demographic characteristics, whereas the health status did not differ between the genders. In particular, Chi square tests for independence indicated significant association between the gender of PD patient and: education level [ $\chi^2$  (3, n= 190) = 7.84,  $p = .049$ ], employment status [ $\chi^2$  (6, n= 189) = 26.21,  $p = .000$ ], and marital status [ $\chi^2$  (4, n= 189) = 15.85,  $p = .004$ ]. Specifically, the proportion of males (66.1%) was much higher in 'tertiary education'; 'employed for wages' (64.7%), 'self-employed' (77.8%), 'retired' (62.5%); and 'singles' (81.8%). On the contrary the proportion of females was much higher in 'household occupation' (90%); 'widowed' (70.6%); and 'in relationship' (100%).

### 6.3.2. Section B, C, D and E

Descriptive statistics summarised respondents' answers to all the items of section B-E, as seen in table 6.4 (pp. 101-102). The horizontal axis includes the questions; whereas the vertical the five response options, as written in the questionnaire. Three extra columns were added on the right: one entitled 'N/A' to sum the number of no answered questions, one '5-7 days a week' to sum up the responses that were at least five days a week (responses: 'often', and 'always'), and one '0-2 times a week' to sum up the responses that were up to twice a week (responses: 'never' and 'occasionally'). Thus, the two last columns revealed the restrictions of mobility and emotional disturbances that appear almost daily (at least five days a week) or rarely (up to two days a week).

**Table 6.4.** Responses to questions of sections B, C, D and E.

Item	Question	Never (0 days a week)	Occasionally (1-2 days a week)	Sometimes (3-4 days a week)	Often (5-6 days a week)	Always (7 a week)	N/A	5-7 days a week	0-2 days a week
	Due to PD, how often during the last week have you....								
B.01	Had difficulty taking the first step when you begin walking?	42	44	47	30	22	07	52	86
B.02	Taken smaller steps when walking, which get faster as you walk?	45	45	44	30	14	14	44	90
B.03	Stopped suddenly while walking without any specific reason?	78	39	32	15	8	20	23	117
B.04	Had difficulty turning in a forward position?	51	36	40	31	17	17	48	87
B.05	Had difficulty remaining upright when walking?	60	34	36	24	27	11	51	94
B.06	Noticed no swinging of the arms during walking?	51	38	43	24	17	19	41	89
B.07	Had a fear of falling during walking?	38	38	34	35	37	10	72	76
B.08	Had difficulty walking upstairs?	63	36	27	15	35	16	50	99
B.09	Had difficulty walking down stairs?	67	32	23	18	34	18	52	99
B.10	Felt stiffness in your legs when walking?	67	38	21	28	16	22	44	105
B.11	Had difficulty walking on a slippery (e.g. wet) or an uneven (e.g. rocky ground) surface?	39	42	38	25	33	15	58	81
B.12	Had difficulty in deep breathing while walking?	68	48	33	17	11	15	28	116
C.01	Had difficulty standing up from a chair?	44	36	39	35	30	8	65	80
C.02	Had difficulty sitting down on a chair?	66	38	36	21	19	12	40	104

Item	Question	Never (0 days a week)	Occasionally (1-2 days a week)	Sometimes (3-4 days a week)	Often (5-6 days a week)	Always (7 a week)	N/A	5-7 days a week	0-2 days a week
	Due to PD, how often during the last week have you....								
C.03	Had difficulty getting into a bed?	61	26	36	34	22	13	56	87
C.04	Had difficulty getting out of a bed?	40	35	33	43	29	12	72	75
C.05	Had difficulty rolling to each side in bed?	44	36	34	35	31	12	66	80
C.06	Had tendency to lean to one side when sitting?	69	24	29	22	31	17	53	93
D.01	Had difficulty writing a sentence on a paper?	46	39	41	31	19	16	50	85
D.02	Had difficulty turning the page of a book?	80	41	33	12	11	15	23	121
D.03	Had difficulty getting dressed or undressed yourself?	54	27	46	31	23	11	54	81
D.04	Had difficulty taking a bath or shower yourself?	66	38	29	17	26	16	43	104
D.05	Had difficulty brushing your teeth?	87	35	24	20	9	17	29	122
D.06	Had difficulty cutting up your food?	60	39	34	27	19	13	46	99
D.07	Had difficulty reaching something above your head?	59	33	31	25	30	14	55	92
D.08	Had difficulty reaching something on the ground?	42	25	37	38	28	22	66	67
E.01	Felt unable to experience pleasure?	33	49	43	39	8	20	47	82
E.02	Thought that things will never improve?	25	38	48	40	24	17	64	63
E.03	Felt angry for apparently minor reasons?	60	43	35	30	4	20	34	69
E.04	Felt isolated and lonely?	57	45	27	27	13	23	40	67
E.05	Felt embarrassed due to having Parkinson's disease?	87	21	23	20	17	24	37	60
E.06	Felt loss of interest about what is happening around you or in doing things?	59	51	25	20	13	24	33	58
E.07	Had problems with your concentration (e.g. when watching TV)?	67	40	30	23	6	26	29	59
E.08	Felt loss of memory?	68	44	26	22	7	25	29	55
E.09	Experienced sleep problems (problems in falling asleep or frequent awakenings during the night)?	33	35	43	30	32	19	62	105

Abbreviations. B: walking; C: transfers; D: hand activities; E: emotional well-being; N/A: no answer; PD: Parkinson's disease.

Table 6.4 (pp. 101-102) showed that all the activities and emotions that were included in the questionnaire, were affected in some way due to PD. The number of responses of each item of the column '5-7 days a week' ranged from 23 (12% of respondents) (items B.03 and D.02) to 72 (37.5%) (items C.04 and B.07). Analytically, the responses '5-7 days a week' in section B ranged from 23 (12%) (item B.03) to 72 (37.5%) (item B.07); in section C from 40 (20.8%) (item C.02) to 72 (37.5%) (item C.04); in section D from 23 (12%) (item D.02) to 66 (34.4%) (item D.08); and in section E from 29 (15%) (items E.07 and E.08) to 64 (33.3%) (item E.02). The most ticked items of each section (B-E) for the columns '5-7 days a week' and '0-2 days a week' are shown in table 6.5, representing the most and less prevalent disability of each section respectively.

**Table 6.5.** The most ticked items of each section for the columns '5-7 days a week' and '0-2 days a week'.

Section	5-7 days a week			0-2 days a week		
	Code	Question	No of responses	Code	Question	No of responses
B	B.07	...had a fear of falling during walking?	72	B.03	...stopped suddenly while walking without any specific reason?	117
C	C.04	...had difficulty getting out of bed?	72	C.06	...had difficulty sitting down on a chair?	104
D	D.08	...had difficulty reaching something on the ground?	66	D.05	...had difficulty brushing your teeth?	122
E	E.02	...thought that things will never improve?	64	E.08	...felt loss of memory?	112

Abbreviations. B: walking; C: transfers; D: hand activities; E: emotional well-being; No: number.

In addition, the ten most common reported restrictions in mobility and emotional disturbances at least five days a week, are reported in table 6.6 (p. 104). As see in the table, four of them were from Section C, related to transfers, and two of each from the rest sections.

**Table 6.6.** The ten most common reported restrictions in mobility and emotional disturbances at least five days a week.

Code	Question	No of responses	Proportion (%)
B.07	Had a fear of falling during walking?	72	37.5%
C.04	Had difficulty getting out of a bed?	72	37.5%
C.05	Had difficulty rolling to each side in bed?	66	34.3%
D.08	Had difficulty reaching something on the ground?	66	34.3%
C.01	Had difficulty standing up from a chair?	65	33.9%
E.02	Thought that things will never improve?	64	33.3%
E.09	Experienced sleep problems (problems in falling asleep or frequent awakenings during the night)?	62	32.3%
B.11	Had difficulty walking on a slippery (e.g. wet) or an uneven (e.g. rocky ground) surface?	58	30,2%
C.03	Had difficulty getting into a bed?	56	29.2%
D.07	Had difficulty reaching something above your head?	55	28.6%

Abbreviations. B: walking; C: transfers; D: hand activities; E: emotional well-being; No: number.

#### 6.4. Qualitative analysis

Thirty two respondents, 11 PD patients and 21 caregivers, provided additional comments at the end of the questionnaire. The comments were coded and grouped into four main categories (motor symptoms and disabilities, non-motor symptoms, medication and beliefs); and in turn, into further subcategories. All the main categories and their subcategories are presented in table 6.7 (p. 105). The subcategories of 'motor symptoms' were related to sections B to D of the survey, to enrich the answers of those sections. In addition, although PD is considered a movement disorder, the comments of six respondents were referred only to the non-motor symptoms of the disease.



**Table 6.7.** Categories and subcategories of the qualitative analysis.

Categories	Subcategories
Motor symptoms and disabilities	Walking
	Transfers
	Hand activities
	Additional motor symptoms
Non-motor symptoms	Mood disturbances
	Sleep disturbances
	Cognitive impairment
	Additional non-motor symptoms
Medication	
Beliefs	Beliefs about the disease
	Survey's criticism

#### 6.4.1. Motor symptoms and disabilities

##### *Walking*

Eleven respondents reported gait disturbances. Difficulty in first steps and poor balance were the major reported signs. Specifically, difficulty initiating the first steps was the most reported walking feature (n= 5). It was more noticed after sitting for a long time (n= 3), and when getting out of the bed (n= 1). During the first steps, the stride length was reduced, and the walking velocity was slow (n= 2).

Five individuals reported postural instability. It was described as *"...the major daily difficulty"* (P72), and as a feeling that *"...somebody pushes me to fall down"* (P17). In addition, two individuals stated frequent indoor falls due to impaired balance. Fear of falling (FOF) was reported by four patients. In particular, one individual had reduced the outdoor activities when raining, and one needed assistance in order to take a shower. Other activities with increased risk for falling included: walking downstairs (n= 1), and when going to the church (n= 1). Lastly, two patients were using a walking stick due to FOF.

The following walking disturbances were reported by one individual each: tremor in the hand while walking; leg rigidity; disability in walking sideways; and fatigue after walking for a while. However, one patient in spite of the minor gait impairments, she was trying to walk as much as possible: *"...On June 2013, I visited Mystras<sup>12</sup> with some friends. I was walking on the hills for two hours while raining, with only two stops to rest."* (O21).

### *Transfers*

Five respondents added more comments relevant to the items of Section C (transfers). Two patients reported that they had difficulties standing up from a chair, only when the height of the chair was low (n= 1) or only during the morning hours (n= 1). Furthermore, there were bed transfers difficulties only when getting out of the bed in the morning (n= 2) or rolling to each side due to hip pain (n= 1). One individual was not able to get out of the car by herself. Thus, she reduced all her social activities due to the avoidance of going out of her house. Lastly, one patient noticed that the progression of the disease worsened his transfers: *"I have gradually decreased my activities. I feel my legs heavy and my trunk stiff. I cannot stand up from a chair. I need help."* (O9).

### *Hand activities*

Only five respondents provided extra information on questions of section D (hand activities). The reported disabilities, and the number of responses are presented in table 6.8 (p. 107). It seems that the restrictions on hand activities affect patients' psychology and decrease their independence. One female stated about her father: *"My father is disappointed. Parkinson destroyed his calligraphy. His letters are not readable...He is unable to get dressed most days and feed himself. My mum helps him daily."* (P139). The possible causes of disability in hand activities were not reported; apart from one respondent, who stated that he was unable to shave himself due to hand tremor. On the contrary, one female reported that the hand disability had been reduced since using special living aids for PD population (ergonomic cutlery set: knife, fork and spoon).

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<sup>12</sup> Fortified medieval town situated on Mount Taygetos, Peloponnese

**Table 6.8.** Disabilities related to hand activities and number of responses.

Disabilities related to hand activities	Number of responses
Dressing (wearing socks)	2
Dressing (tying shoes' laces)	1
Facial shaving	1
Micrographia <sup>13</sup>	1
Shower	1

### *Additional motor symptoms*

Three respondents stated more general motor-symptoms (primary motor symptoms of PD) that cannot be included into the previous subcategories: dystonia (n= 2), tremor (n= 1), bradykinesia (n= 1). These symptoms are also considered disturbing either by the patient or the carer: *"The tremor in the hand and leg are among the worst symptoms. I can hardly relax."* (O17); *"My husband makes unexpected movements while sitting or sleeping...He kicks and throws punches...I 'm afraid of my safety."* (P87). One PD patient noticed relapse of the motor-symptoms during the night; before going to bed.

### 6.4.2. Non-motor symptoms

The respondents reported non-motor symptoms related to all the categories, as proposed by van Laar and Jain (2004) and Pandya et al. (2008) (sensory, autonomic, cognitive-behavioural, sleep disorders).

### *Mood disturbances*

Mood disturbances were the most reported non-motor symptom of PD (n= 10). Three patients reported depressive symptoms, whereas two were clinically diagnosed with depression. Loss of interest (n= 1), thought that things will never improve (n= 1), low self-esteem (n= 1), were the reported signs of depression. In three cases, depressive symptoms were combined with hallucinations. One caregiver stated visual hallucinations: *"My father*

<sup>13</sup> Abnormally small handwriting or handwriting that becomes progressively smaller

*sees friends and relatives from the past, robots and strange creatures in the house and garden.” (P139).*

Five patients suffered from anxiety signs. None of them reported any diagnosed anxiety disorder. One caregiver reported general phobia and high levels of stress, whereas in two individuals high levels of stress were associated with tremor. A patient reported symptoms of social anxiety disorder; as he was avoiding social situations, due to feelings of embarrassment about PD. Three patients expressed concerns about their future. It seems that the ongoing financial crisis of the country contributed to their high anxiety levels. They were worried whether they would be able to pay for a caregiver (n= 1), buy their PD medication (n= 2), and cover the healthcare services (n= 1). One PD patient wrote: *“My income has been reduced. Taxies are rising up. PD is a disease for rich people. Healthcare services and medication are so expensive! I cannot afford to pay them.” (P83).*

Finally, two respondents reported mood fluctuations during the day, and one caregiver abilities self-overestimation. He/She wrote: *“My father has reduced his mobility due to PD. However, he believes that he is able to take the metro and go for a walk in the city centre. He often wants to drive his car.....He doesn’t understand the severity of his symptoms.” (O3).*

### *Sleep disturbances*

Sleep disturbance seemed to be a serious problem among the respondents. Six individuals reported sleep disturbances as follows: intense and sudden movements during sleep (n= 3); insomnia (n= 2), vivid dreams and nightmares (n= 2), difficulties falling asleep (n= 2), early morning awakening (n= 1), and excessive daytime sleepiness (n= 1). A carer wrote: *“I cannot sleep during the night....sometimes his movement are so intense! He often speaks loudly while sleeping.” (P48).* Lastly, one patient wrote: *“One of my major problems, since I was diagnosed with PD, is insomnia. Sleeping pills help me to sleep; otherwise I may fall asleep on the daytime while sitting on a sofa.” (P17).*

### *Cognitive impairment*

Cognitive deficits were a major complaint of PD caregivers (n= 4). According to them, two PD patients had been diagnosed with dementia. Additional reported impairments were: short-term memory loss (n= 2), slowed thinking (n= 1), inability to remember to take their PD medication (n= 2), confusion in remembering names (n= 1), poor vocabulary (n= 1), difficulty in finding the right word into a sentence (n= 1). Due to cognitive impairments some patients were at risk: *“My dad forgets to take his medication. He usually does not remember how to use the tap and open a window. My mother looks at him 24 hours a day.”* (P155).

### *Additional non-motor symptoms*

Eleven respondents reported additional non-motor symptoms that could not be included in the previous categories. These symptoms are presented in table 6.9 (p. 110). Hypophonia seems to be a disabling symptom that affects the communication of patients: *“I speak in a low voice.....the others do not understand what I say, and they ask me to repeat it.”* (P112).

### 6.4.3. Medication

Four people recorded their experience about PD medication, and the improvement or not of the symptoms. In one case, the symptoms were improved significantly: *“I had all the symptoms that are written in the questionnaire. Hopefully due to medication my mobility has changed. I have a great improvement.”* (O13). On the contrary in two cases there was a little improvement some days of the week: *“My father is living with PD the last 23 years. The medication does not often work. Several days he is not able to start walking.”* (P155); *“I have increased my medication to six Stalevo pills....somedays I feel good, some others no.”* (O9). One female reported the side effects of medication: *“Drug treatment caused me gambling. I was addicted. I was going to Mont-Parnes<sup>14</sup> to play.....I lost a lot of money....My family took the keys of my car.....I spoke to my doctor after some months.....He changed my medication...”* (P126).

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<sup>14</sup> Casino on the Mount Parnitha, Attica (Athens).

**Table 6.9.** Additional reported non-motor symptoms.

Sensory symptoms (N=6)	Autonomic symptoms (n= 2)	Speech disturbances (n= 2)	Additional symptoms (n= 2)
Pain (n= 3):	Sialorrhea <sup>15</sup> * (n= 1)	Hypophonia (n= 2)	Fatigue (n= 2)
• low back pain (n= 1)	Sweating (n= 1)**	Imprecise articulation (n= 1)	
• coat hanger pain (n=1)	Sexual dysfunction (n= 1)		
• headaches (n= 1).			
• cramps***			
Hyposmia <sup>16</sup> (n= 1)			
Impaired sense of taste (n= 1)			
Peripheral sensory defect: burning sensation in the hand (n= 1)****			

Abbreviations. n: number of respondents.

\*especially when lying on the bed

\*\*while sitting or lying on the bed

\*\*\*usually while sleeping

\*\*\*\*it was described as “*rubbing a sandpaper on the skin*”

#### 6.4.4. Beliefs

##### *Beliefs about Parkinson’s disease*

Two respondents -one PD patient and one carer- expressed desperation feelings about the disease. One patient described his life as “...hell” (P83) due to PD. A carer’s text was of particular interest: “...because Parkinson’s is an everyday and slow death, not only for the sufferer, but also for the family; I beg you, as specialists, to find the treatment of the disease. It will be our redemption.” (P155). On the contrary two patients were more positive about their future. One individual expressed her determination by writing “...I will not give it up” (O21); whereas another stated: “Congratulations to you against the insidious disease. I wish we became healthy. Things will get better.” (P112).

<sup>15</sup> Excessive drooling

<sup>16</sup> Impaired sense of smell

*Survey's criticism*

Two individuals commented negatively on the survey's design. They noticed that all the questions were referred to the frequency, and not to the degree of difficulty: *"The question D.01 is about writing difficulties. How it is possible to have difficulties only 1-2 days a week and the rest days no? My answer would be that my handwriting has changed. This activity is quite difficult for me and is getting worse."* (P5). Furthermore, another patient believed that it would be better to split the questions for the on- and off-state of the disease. Hence, the answers would differ: *"I 'm getting dressed easily during the on-state, but I have difficulties to dress myself at the off-state."* (P17).

**6.5. Summary of Chapter 6**

- 192 questionnaires were totally included in the analysis section.
- Almost half of the respondents were carers of PD patients.
- With respect to the socio-demographic characteristics, the majority of patients were males (55.2%), Greeks (96.9%), were living in Attica (Athens Metropolitan Area) (68.2%), were retired (66.1%), and their mean age was 68.31 years.
- Regarding the health status: the median duration of PD since diagnosis was four years, 97.2% were under antiparkinsonian medication, only 28.7% reported significant improvement of PD symptoms due to pharmacological treatment, and 92.7% reported comorbidities.
- All motor sections (walking, transfers, hand activities) and emotional well-being were affected in some way due to PD.
- The most prevalent reported disabilities (at least five times a week) were: FOF, getting out of bed, rolling to each side of the bed, reaching something on the floor, standing up from a chair.
- The most common emotional disturbance was that "things will never improve".
- Only 32 respondents answered the last open-ended question at the end of the questionnaire. Their answers were coded into four categories: motor symptoms, non-motor symptoms, medication and beliefs.

- The answers of the open-ended question revealed that the respondents recognised that PD is characterised by both motor and non-motor symptoms. They also stated that FOF provokes further disability and reduces social activities; they expressed concerns about their future due to the ongoing financial Greek crisis; and believed that the antiparkinsonian medication has side effects and is not always effective in controlling the motor symptoms.



# **CHAPTER 7**

## **SURVEY - DISCUSSION**

### 7.1. Main findings – summary of key results

Everyday activities of people living with PD are particularly challenging, and they also face a variety of emotional disturbances. As far it is known, no study has been found to detect the level of mobility, and emotional status in Greek population with PD. Thus, the current mixed mode survey was conducted. The level of mobility was assessed using items relevant to basic ADLs, whereas the socio-demographic profile and health status of patients were also recorded. This was an important source of information, as it provided an in depth understanding of the target population, in order to design the intervention of the present RCT.

Overall 192 questionnaires, completed by patients with PD or their carers, were included in the analysis section. The results demonstrated restrictions both in physical function and emotional well-being. FOF (item B.07) and 'difficulties in getting out of bed' (item C.04) were the chief complaints. Four out of ten most prevalent restrictions were related to transfers (items C.01, C.03, C.04, C.05), two to walking (items B.07, B.11), two to hands activities (items, D.07, D.08), and two to emotional well-being (items E.02, E.09). However, it is noticeable that the two most affected hand activities (items, D.07, D.08) require a high level of static balance, and may indicate balance impairments.

The open-ended question at the end of the instrument revealed that the patients and their carers recognised that PD has both motor and non-motor symptoms, which impact their life. Some individuals did not notice any significant improvement of cardinal symptoms, due to antiparkinsonian medication, whereas they reported side effects of medication. Some of respondents were pessimist about their future, expressing feelings of desperation. Lastly, they expressed concerns whether would be able to afford the high cost for the management of the disease, due to the ongoing debt crisis.

## 7.2. Interpretation of findings

### 7.2.1. Socio-demographic characteristics

In the current survey, the proportion of males (55.2%) was slightly greater than females (44.8%). These results are in accordance (males 57%, females 43%) with a study conducted in Greece (Konitsiotis et al., 2014), and findings from other studies supporting that men are more likely to be diagnosed with PD worldwide (de Lau and Breteler, 2006; Wirdefeldt et al., 2011). The less prevalence of PD in females could be explained by the higher initial striatal DA levels in women, and the protective role of oestrogens against nigrostriatal degeneration (Miller and Gronin-Golomb, 2010). On the contrary, males may be most exposed to environmental factors (e.g. toxins) that are associated with the onset and development of PD (Antony et al., 2013). However, as females are typically less likely to refuse a survey invitation than males (de Leeuw et al., 2008), the proportion of male population affected by PD could be even higher.

The mean age (SD) of PD patients was 68.31 ( $\pm$  10.39) years, range 42-88. Similar findings (mean age: 70.4 years) in Greece were also reported by Konitsiotis et al. (2014). In the present study, only 4.2% of patients were between 40 and 49 years. This is also supported in the literature, as the prevalence rate of PD increases steadily with age, being extremely rare in those under the age of 50 years (Pringsheim et al., 2014; Elbaz et al., 2016). The increasing prevalence of PD with age may be associated with age-related changes in the neurotransmitter system. In particular, it has been reported decline in DA synthesis in many brain areas due to aging, which may speed up the onset of motor symptomatology of PD in senior population (Desai et al., 2010).

In addition, the vast majority of patients with PD had Greek nationality (96.9%). The number of patients with non-Greek nationality was expected to be higher; because according to the official last population census in 2011, 8.3% of the population in Greece were immigrants (Hellenic Statistical Authority, 2014a). However, Greece has become a final destination for immigrants since the 1990s (Antonopoulos and Winterdyk, 2006), and around 90% of them are younger than 60 years (Hellenic Statistical Authority, 2014b);

whereas PD affects mainly individuals over 60 years (Elbaz et al., 2016). Furthermore, the proportion of immigrants, which were able to read and write in Greek in order to complete the current questionnaire, was unknown. Lastly, similarly to other countries; it may be under debate whether ethnic minorities and immigrants (especially undocumented immigrants) in Greece have limited access to the healthcare system facilities (Wirdefeldt et al., 2011), preventing them to complete the current questionnaire through the HPDA.

Regarding the place of residence, 78.1% of patients were living in urban areas. This is in line with the Hellenic Statistical Authority, as the urban population in the country was 76.6% in 2011 (Hellenic Statistical Authority, 2014a). However, residents of two administrative regions (Ionian Islands and Western Macedonia), representing 4.47% of the country's population, did not complete the questionnaire. In addition, the questionnaire was completed only by one individual each living in Crete and in Eastern Macedonia- Thrace, which represent 11.42% of Greece's population (Hellenic Statistical Authority, 2014a). Despite the fact that the paper survey was conducted in Athens Metropolitan Area, 43 of 164 questionnaires were referred to patients living in other administrative regions. This may be explained by the fact that Greek citizens living in small cities or rural areas visit the two large cities (Athens, Thessaloniki) of the country at least once a year for personal issues, such as medical reasons. Indeed, some patients that participated in the paper survey, reported verbally to the researcher that they were in Athens to visit their neurologist- PD specialist. In addition, a significant proportion of retired individuals in Greece share their time between their main residence in urban areas and their secondary residence in the countryside, which is usually their place of origin.

With respect to the employment status, the majority of patients (66.1%) were retired, whereas only a small proportion was unable to work due to PD (2.1%). The retirement age for both genders in Greece was 65 years up to 2013, 66 in 2014, and 67 since 2017. However, in the current study, 18 individuals younger than 65 were retired. This may partly be explained by the fact that in the past some categories of citizens enjoyed early retirement. Indeed, the retirement age for women was 62 years; whereas for the "heavy

and unhealthy jobs” (βαρέα και ανθυγιεινά επαγγέλματα), as being characterised by the Greek Constitution, 57 years. Furthermore, individuals with overall disability rate at least 67% could apply for early retirement. Lastly, it was unknown whether the participants of the current survey were fully or partially retired.

### 7.2.2. Health status

Despite the fact that only patients with PD were included in the study, it was impossible to know whether the respondents gave an accurate response about the disease. As there was not any clinical examination to confirm the diagnosis of PD; there is danger that the sample may have included participants suffering from other forms of Parkinsonism, apart from PD; such as progressive supranuclear palsy, multiple system atrophy and essential tremor. Based on empirical knowledge, in Greece some individuals with other causes of tremor, often mistakenly state that they suffer from PD. The fact that 97.9% of the sample received L-dopa medication, is an indication of PD. However, improvement of symptoms due to dopaminergic medication is also seen in multiple system atrophy (Jankovic, 2008). Lastly, it is unsure whether newly diagnosed patients (up to three months) were suffering from PD, as the negative response to dopaminergic medication is an exclusion criterion for PD (NICE, 2006).

With respect to antiparkinsonian medication, a significant proportion (65.3%) of respondents admitted that the symptoms did not significantly improved due to antiparkinsonian medication. The reasons for this response may be multifactorial. Firstly, the answer is totally subjective, based on the respondent’s opinion. Secondly, evidence supports that in patients at advanced stages, the medication is not always effective; maybe due to motor fluctuations (Pedrosa and Timmermann, 2013). Another issue of antiparkinsonian drugs are the side effects of medication, some of them being serious (Rao et al., 2006). Indeed, one patient reported the development of pathological gambling, which may have been a side effect of DA agonists (Alonso Cánovas et al., 2014).

The results revealed that the vast majority of patients (92.7%) were also suffering from additional comorbidities, apart from PD. A direct comparison with the findings of the study by Konitsiotis et al. (2014), which was held in Greece, was not feasible; as only the most prevalent comorbidities were reported in their study. The increased number of comorbidities in the present survey, may be explained by the fact that PD is more prevalent in third age (over 60 years), which is linked with aging-associated disorders (Elbaz et al., 2016).

Despite the fact that anxiety and depression are considered among the most prevalent non-motor symptoms in PD; only three individuals reported -at item A.16 (additional medical conditions) or the open-ended question at the end of the questionnaire- depression as comorbidity, and none anxiety. This proportion is below the mean prevalence of depression in PD (Perrin et al., 2017). However, at the end of the questionnaire ten respondents stated mood disturbances due to PD. It is unknown whether the respondents did not report any mental disorder due to stigma arising from their diagnosis, or an existing mental disorder has not been recognised yet (Section 3.6.4).

In addition, none of the respondents stated how depression was clinically diagnosed. This may be explained by the fact that the survey did not include any relevant item. Although the DSM and ICD criteria are considered the gold standards for the diagnosis of mental disorders (Jacob, 2006), empirical knowledge supports that this is not the case in Greece. The diagnosis of anxiety and depressive disorders is often performed by medical doctors (such as pathologists and neurologists), who prescribe medication for their management, rather than experienced psychologists and psychiatrists.

### 7.2.3. Motor restrictions

All the respondents stated impacts of PD on ADLs (sections B-D); which indicate that the disability arising from the disease is evident and well recognised, by the patients or their carers, even in the first stages of the disease. However, it was not possible to detect the

section (B, C, D) that was more affected, as the distribution of responses seems to not differ significantly between the three sections.

### *Walking*

190 individuals (99% of respondents) reported at least one gait disturbance at section B, due to PD, whereas only two newly diagnosed patients did not experience any difficulty. This is in line with the gait analysis study by Kang et al. (2005), which revealed that 87% of patients with PD had gait impairments, even from the first stages of the disease. Although both FOG and festination signs were reported, it seems that the main concern of patients was by far the FOF (item B.07). The aetiology of increased FOF in PD may be multifactorial. FOF is aggravated by the symptoms of the disease (i.e. postural instability, gait disturbances), restrictions in ADLs (i.e. transfers), previous falls, aging, increased levels of anxiety and depression. In turn, FOF may provoke further disability, as the patients usually restrict further their ADLs to avoid a fall, and may have significant impacts on QoL (Rahman et al., 2011). Indeed, one patient wrote that her ADLs were reduced due to FOF, whereas two patients were using a walking stick to avoid a fall.

Walking on a slippery or uneven surface (B.11) was the second most common reported disability, indicating balance impairments. The maintenance of balance under these conditions is extremely difficult; because there is little or no friction, and often redirections of the body centre of mass compared to smooth terrain. In order to maintain the upright position and avoid a fall, there are increases in the variability of step width and length, and high energy expenditure due to the co-activation of muscles (Voloshina et al., 2013).

Disabilities related to FOG (items B.01, B.03, B.04), festination (items B.02, B.06), and rigidity (items B.05, B.10), which may lead to postural instabilities, were also reported. In turn, postural instability seems to be the major intrinsic factor leading to falls, along with the severity of the disease and ageing (Pandya et al., 2008). Indeed, in the current survey, two individuals stated frequent indoor falls due to impaired balance.

On the contrary, only 28 patients experienced difficulties in deep breathing while walking (item B.12) at least five days a week. In PD, flexed posture, due to rigidity, may decrease the strength of the diaphragm and the secondary inspiratory muscles of the upper thorax (Baille et al., 2016). In addition, bradykinesia may lead to difficulties in performing relative fast and repetitive thoracic movements (Kolesnikova, 2006). These factors may cause a restrictive disorder, usually in the moderate and advanced stages of the disease (H&Y stage three to five). However, as the patients restrict their daily activities -due to the motor symptoms of the disease-, they rarely notice respiratory impairments and report them to their physician (Baille et al., 2016).

### *Transfers*

The findings of Section C revealed that transfer activities from/to chair and bed were affected to some extent due to PD. However, 12 respondents 'never' had any transfer difficulty. Transfers are complex movements, involving several joints, which are carried out in a sequence. Although restrictions in transfers may start even from the first stages of the disease, they become more apparent as the disease progresses. Although the exact mechanism of transfer disability remains unknown; it seems that muscle weakness, decreased ROM, and postural deformities due to rigidity may play a role (Keus et al., 2007). Biomechanical analysis in patients with early PD revealed that, in order to facilitate rising from seated position, they performed small movements of the trunk in the sagittal plane with higher velocity, to develop greater forward momentum, allowing them to stand up (Nikfekar et al., 2002).

Based on the answers of respondents, 'standing up from a chair' (item C.01) and 'getting out of a bed' (item C.04) were more affected than 'sitting down on a chair' (item C.02) and 'getting into a bed' (item C.03); probably because these movements are against gravity, and may require more patients' effort. With respect to the item C.05 (rolling to each side on bed), high-friction bed sheets and clothing (i.e. cotton sheets) may make the rolling movements more difficult. In addition, during the night and early morning hours the medication is reduced making the movements more difficult. Lastly –although it is not



considered a transfer activity-, 106 patients experienced 'tendency to lean to one side when sitting' (item C.06). This is an indicator of 'Pisa syndrome', which may affect balance and lead to falls (Heisters, 2011).

#### *Hand activities*

178 respondents stated impaired hand activities (section D). Reaching activities (items D.07 and D.08) were the most common reported disabilities of Section D. These activities require a satisfactory level of balance, as the base of support is reduced and the body centre of mass is usually beyond the base of support. Despite the fact that difficulties in writing and micrographia are among the early signs of PD (Jankovic, 2008), 46 individuals were free of writing difficulties (item D.01). Perhaps, patients with writing or typing difficulties were not able to complete the questionnaire.

The causes of hand restrictions in PD may be due to the principal motor symptoms of the disease (bradykinesia and rigidity). Despite the fact that one patient reported tremor as the source of disability; tremor in PD has no correlation with disability, as it is usually at rest and stops when performing voluntary movements (Muslimović et al., 2008; Shulman, 2010). In addition, it was unknown whether special equipment was used by patients to improve fine motor skills (items D.03, D.05 and D.06), and to avoid a fall while taking a shower (item D.04); or whether assistance was provided by another person. Only one respondent stated that assistance was required to take a shower due to FOF, and another that special equipment was used for eating.

#### 7.2.4. Non-motor symptoms

##### *Emotional health*

Mood disturbances due to PD were reported by almost all the respondents at section E, apart from two individuals. In addition, they were the most common reported non-motor symptoms at the open-ended question at the end of the instrument. This is not surprising considering the high prevalence of anxiety and depressive disorders in PD (Perrin et al.,

2017). However, it seems that the emotional well-being of patients has been also affected by the ongoing debt Greek crisis. An interesting fact is that the number of non-answered items in section E was much higher than the other sections of the questionnaire (A-D). Indeed, the average number of non-responses for each item of section E was 22, whereas in the other sections varied from 12.3 (Section C) to 15.5 (Section D). Evidence supports that higher non-response rate is usually seen in the items that are placed at the end of the questionnaire (Galesic and Bosnjak, 2009). Furthermore, some questions related to the emotional well-being may have been considered embarrassing or particularly sensitive by the respondents; and hence, they were not answered (Fan and Yan, 2010).

The answers revealed that generally the frequency of depressive symptoms (items E.01, E.02, E.04, E.06) was higher than anxiety symptoms (items E.03, E.05, E.07). The less reported item of section E was E.05. In particular, 87 patients were free of embarrassment due to PD, which is linked with social anxiety disorder (SAD). Hence, the respondents may have not restricted their social activities, due to the lack of stigma arising from the signs of the disease (Chiong-Rivero et al., 2011). However, based on their statements at the end of the questionnaire, social restriction has arisen, due to FOF and impaired mobility. Despite the fact that the questionnaire included only items relevant to general anxiety disorder (GAD) and SAD, which are more prevalent in PD (Broen et al., 2016); one patient reported symptoms of phobia at the end of the questionnaire, indicating that almost all the anxiety disorders could be present in PD. Lastly, one patient experienced tremor while walking. This may indicate anxiety. Although the exact mechanism is not known, empirical evidence supports that anxiety disorders seem to exacerbate PD tremor, especially during the off-period (Heisters, 2011).

In addition, 99 and 140 patients experienced 'loss of memory' (item E.08) and sleep disturbances (item E.09) respectively. Loss of memory is an indicator of cognitive deficits. Both cognitive impairments and sleep disturbances are linked with anxiety and depression (Pachana et al., 2013). Specifically, depression has been identified as a risk factor for dementia, maybe due to similar biological mechanisms for their onset (i.e. damages in

common brain areas). On the contrary, depression could also be a reaction or a psychological response to the diagnosis of cognitive impairment (Muliya and Varghese, 2010). Although sleep disorders and cognitive deficits are highly prevalent in mental disorders; their causes in PD are numerous, including the neurodegeneration process itself, which can disrupt the networks regulating the sleep–wake and affect brain regions involved in cognition (i.e. prefrontal cortex and limbic system). Additional factors for sleep disturbances in PD include: pain, nocturia<sup>17</sup>, dystonia, bradykinesia, difficulty turning on bed, reactions to medications, and vivid dreaming (Pachana et al., 2013). Thus, it is not possible to support that items E.08 and E.09 are solely linked with anxiety and depression.

It was also reported at the end of the questionnaire that three patients suffered from hallucinations, which is a sign of psychosis. However, the source of psychosis in PD is complicated; and not just a symptom of severe depression or schizophrenia. It may also be a natural outcome of the disease, due to increase of serotonergic activity and, greater Lewy body presence in the amygdala and cortical area; and a side effect of antiparkinsonian medication and DBS. There is also an association between sleep disturbances in PD and hallucinations, because sleep disturbances may lead to altered dream phenomena, which later lead to daytime hallucinations and delusions (Zahodne and Fernandez, 2008).

#### *Additional non-motor symptoms*

Despite the fact that it is supported in the literature that the non-motor symptoms of PD are often under-recognised and poorly treated (Goldman and Postuma, 2014); some patients apart from emotional disturbances (Section E), reported sensory and autonomic symptoms, speech disturbances, cognitive deficits and sleep disturbances. Nowadays, it seems that the patients and their families are more well-informed about PD. In Greece, apart from internet which offers access to specialised international websites about PD; it seems that the actions of the two PD organisations (Section 2.7) may have played a role. Indeed, their webpages and booklets provided in the Greek language, and the organisation

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<sup>17</sup> Excessive urinating at night

of symposiums may have improved the knowledge of Greek citizens about the disease and its management options.

#### 7.2.5. Beliefs

Only four respondents expressed their beliefs about the disease. This prevents the export of strong conclusions about the beliefs of Greek patients living with PD and their carers about the disease. The findings were controversial; with two participants being optimists, and two pessimists about their future. The sociocultural model supports that the beliefs in chronic illness may be influenced by cultural and social determinants. These may include: education, income, access to healthcare, previous experiences, stigma arising from the disease, response to treatment, support from the family, and knowledge about the disease (Chin and Noor, 2014). Indeed, in the current study one patient who described his daily life as “hell” (P83) due to PD; stated previously that it was hard for him to afford the cost of treatment, as his income had been reduced. It seems that the ongoing Greek crisis, characterised by cuts in health domain and reductions in citizens’ income, has affected the levels of optimism of patients and their caregivers. In turn, evidence in PD supports that illness beliefs are important predictors on psychological outcomes and physical functioning (Simpson et al., 2013), and they may affect treatment compliance (Chin and Noor, 2014).

### **7.3. Comparison with previous studies**

The findings of the present survey are partly in line with those of previous studies supporting that PD is characterised by impaired physical functioning, loss of independence and emotional consequences (de Boer et al., 1996; Brod et al., 1998; Findley, 1999; Chiong-Rivero et al., 2011; Konitsiotis et al. 2014; Uebelacker et al., 2014). The combined results of these studies indicated that the chief complaints of patients and their caregivers were: difficulties in manual motor skills (writing, dressing, bathing, grooming), transfers (getting up from a chair, getting out of bed, turning around on bed) walking (turning while walking), balance impairments, anxiety and depressive symptoms (e.g. low self-esteem, feeling embarrassed due to PD, being afraid of possible disease progression, very sensitive-easily driven to tears), sleep disturbances, difficulties with concentration, fatigue and dysarthria.

However, a direct comparison between the findings of the current survey with those trials is hard to be done, due to the different methods used to assess the restrictions. Although their aim was to identify the demographic characteristics and assess the emotional and physical health, based on the symptoms of the disease and some basic ADLs; different measurement tools were selected. The researchers did not assess the frequency of disabilities, apart from Findley (1999). Brod et al. (1998) used Parkinson's Problem Schedule Questionnaire to detect the motor disability and they built a questionnaire to assess the emotional status through a semi-structure interview. In the study by Chiong-Rivero et al. (2011), participants were asked to answer open-ended questions about their physical functioning. In one trial (Konitsiotis et al. 2014), patients were requested to classify the severity of tremor, bradykinesia and gait disturbances using a five-point scale. Uebelacker et al. (2014) asked the participants to report the two more bothersome problems due to PD. Lastly, de Boer et al. (1996) did not report the selected questionnaire to assess physical and mental health. Surprisingly, none of the studies with a self-designed questionnaire or interview provided a link to access the tool; and only the most troublesome symptoms/restrictions were reported in the results section (de Boer et al., 1996; Brod et al., 1998; Findley, 1999; Chiong-Rivero et al., 2011; Konitsiotis et al. 2014; Uebelacker et al., 2014). Similarly to the present survey, only in the study by Chiong-Rivero et al. (2011) the respondent could be either PD sufferers or carers of PD patients.

The literature search identified only one trial (Konitsiotis et al. 2014), conducted in Greece to record the clinical characteristics of 986 outpatients suffering from PD all over the country. Based on patients' responses the most troublesome symptom was gait disturbances, followed by bradykinesia. A direct comparison between the results of Konitsiotis et al. (2014) and those of the present study was not feasible, as concerning the physical function, our study assessed specific ADLS and not just the symptoms of the disease. Contrary to the present trial, the sample in the trial by Konitsiotis et al. (2014) may be representative of the Greek PD population, because it consisted of outpatient PD population from all the administrative regions of the country, increasing its external validity.

## 7.4. Methodological issues- strengths and limitations

### 7.4.1. Strengths of the current study

After the interpretation of the study's findings, several strengths must be acknowledged. The instrument was designed to be suitable for use in patients with PD living in Greece, and facilitate the completion and analysis process. Thus, special emphasis was given to the language and the formulation of questions and answers. Close-ended questions were preferred to facilitate: the completion of the questionnaire by PD patients, who may experience difficulties in writing even from the first stages of the disease; and the analysis using quantitative approaches. The socio-demographic questions of section A were consistent with the landscape of Greece (Iarossi, 2006). In order to exclude individuals not suffering from idiopathic PD, terms that are usually written in medical diagnoses in Greece were preferred (Parkinsonism, extrapyramidal syndrome). The evidence-based design and the rigorous methodology aimed to achieve increased response rates, more accurate responses, and decreased blank responses. The conduction of a pilot work aimed to identify errors in the design of the instrument, and in the whole methodology. The fact that the respondent could be either a PD patient or a carer enabled to include in the survey's sample patients, who were not able to complete the questionnaire for a variety of reasons; such as disability in writing, and inadequate computer skills. Lastly, the overcoverage bias was avoided by checking the patients' name to identify whether they appeared twice.

### 7.4.2. Limitations of the current study

#### *High non-response rates (online survey)*

The whole survey design aimed to keep bias at minimum. Nevertheless, the study was not free of limitations. The major limitation was that the online survey produced lower response rates than expected. The high non-response rate may have led to non-response bias, because it is unsure whether the vast majority of people who did not respond would have responded in the same way as those who did. In turn, the non-response bias may have affected the external validity of the study (Brace, 2013).

Non-response may occurred for a variety of reasons. The most influential psychological theories, which could be combined and explain the low response rate in surveys are: the social exchange theory, the social psychological approach, and the leverage–saliency theory. Some individuals may do not trust the surveys (social exchange theory). In some surveys, respondents are not motivated enough to make the participation decision (social psychological approach). Lastly, the potential participants judge all the aspects before taking the final decision to complete or not a questionnaire (leverage–saliency theory) (Fan and Yan, 2010).

Regarding the present online survey; the instrument's design, the delivery process, the potential respondents' attitude and skills, and difficulties in internet acces, may partly explain the low response rates. In particular, the length of the questionnaire may had been long for the target population suffering from a chronic disease, producing fatigue and contributing in increasing public resistance (Brace, 2013). Although the anonymity and the personalisation of invitations and reminders are significant predictors of response rates in online surveys (Fan and Yan, 2010); in the current study, the questionnaire was non-anonymous to check for double-responses, and the invitation and reminder letters were not personalised. Moreover, some items of the questionnaire (i.e. section E -emotional well-being-) may have been considered sensitive by the respondents; triggering embarrassment, stress or pain (Brace, 2013).

In addition, the members of the HPDA are not solely patients with PD; hence the invitation was also sent to individuals free of PD. Some individuals may have also died or been very disabled to answer the questionnaire. The high non-response could have been also caused: by incorrect e-mail addresses; by rare e-mail check; by the recipient's email system judging the e-mail to be spam, and therefore not delivering it; or by the recipient judging the email to be spam and not opening it. Some individuals may have had minimal computer skills to complete the online questionnaire (de Leeuw et al, 2008). In some cases they may have been difficulties with internet connection (something common in rural areas of Greece) or computer access; resulting in a biased sample, and less response rate (Fan and Yan, 2010).

*Additional limitations*

Additional limitations may have been arisen due to the methodology of the present survey; or they may simply reflect the limitations of the selected mode of administration and method of delivery and approach for the data analysis. Firstly, there was lack of statistical power for the main study and the sub-group analysis, which prevented the drawing of strong results and conclusions (Mayer et al., 2015). With respect to the main study, it was decided to stop the survey when 200 completed questionnaires were collected. Thus, the margin error was 7% instead of 5%, and the confidence 84% instead of 95%. Regarding sub-group analysis for males-females, the sample size was calculated only for the primary aim of the study. A sample size determination is required in order to perform a sub-group analysis. Otherwise, the results may not be valid, due to small sample size (Moher et al., 2010).

Coverage bias may have been arisen, because it was impossible to include the entire population of PD patients living in Greece (Tourngeau et al., 2000). In light of the relatively small sample size, and the fact that the paper survey was conducted just in Athens; the sample population may have not been representative of the target population. In addition, the convenience sampling was followed, as the most easily accessible people for the sampling frame were selected (Hicks, 2009). Indeed, there were no representatives from two administrative regions of the country, whereas it seems that the questionnaire did not reach the ethnic minorities and immigrants living in Greece. In addition, PD patients not being members of the HPDA, had zero chance of being included in the sample. Hence, caution is needed for the generalisation of the results.

There were also some additional limitations in the design of the questionnaire. Firstly, PD patients were not consulted for the selection of items. Nevertheless, in the pilot work, patients' responses relevant to daily activities that had been affected due to PD and were not included in the questionnaire, were evaluated. Secondly, with respect to anxiety disorders; Section E consisted only of items relevant to GAD and SAD, whereas items relevant to other types of anxiety disorders (e.g. panic disorder) were not included.



Although in Section E there was an attempt to avoid items relevant to anxiety and depression that may overlap with other core symptoms of PD, this was not always possible. Indeed, difficulties with concentration (item E.07) in PD indicate either anxiety or cognitive impairments, such as dementia (Caballol et al., 2007). Loss of memory (item E.08) in PD is also associated with sleep disturbances; whereas depression, cognitive impairment, and side effects of DA agonists and L-dopa may be the cause of sleep disturbances (item E.09) (Goldman, and Postuma, 2014). In addition, the items of sections B-E assessed just the frequency of restrictions, and not their severity. The questions were also not split for the on- and off-state of medication, in order to keep the questionnaire simple and facilitate the data analysis. This was criticised by some patients, which reported difficulties in performing some activities only during the off-state of medication.

Despite the advantages of self-reported instruments, there are concerns about the findings, which depend completely almost on accuracy of individuals' answers (Tournageau et al., 2000), increasing the possibilities for response and measurement bias (de Leeuw et al., 2008). Cognition, emotional well-being and environmental factors may have affected the accuracy of answers. Regarding environmental factors, patients living with a carer may have reported lower levels of disability (sections B-D), because they could not recognise that they were dependent on others. On the contrary, patients living alone may have overestimated their level of disability, as there was not another individual to provide assistance in case of emergency (e.g. fall) (Shulman et al., 2010). Despite the fact that in sections B-E the respondents were not forced to report events that had happened too long ago, some may have had difficulties remembering exact dates, reporting events that took place before the specified reference period. Thus, there is danger for telescoping bias, a category of recall bias (Tournageau et al., 2000). In addition, in surveys some respondents have the tendency to give social desirable answers instead of reporting the truth, especially in sensitive topics; producing social desirability bias (Cook and Campbell, 1979).

Furthermore, it is unclear whether the responses of carers could have led to response bias, as those carers who hold particularly strong views on the health status of patients are more

likely to respond. In addition, it is unsure that the carers, who completed the questionnaires, were objective about the level of patients' disability and emotional status; hence, they may have underestimated or overestimated their health status (Greenwood et al., 2010). This is of particular interest in the Greek society, as the carers usually are the husband/wife and the children of the patients, which may spend few hours with him/her. Lastly, as the current study was a mixed-mode survey, it was unclear which mode of questionnaire was associated with more accurate answers. It is supported in the literature that it is unclear whether the questions are answered differently online compared to more traditional methods, such as self-administrated paper based questionnaires (Iarossi, 2006).

An interesting fact was that only 32 of 192 respondents completed the open-ended item at the end of the questionnaire; whereas only 11 of them were PD sufferers. The low response rate of this question may be related to the fact that the completion of long open-ended questions demands literacy and a relative high level of active command of a language. Hence, respondents in order to avoid grammatical inhibited the freedom of expression, or did not answer the current question (Bradburn et al., 2004). In addition, respondents were likely to be unwilling to take the time to answer this question (Choi and Pak, 2005). The writing or typing difficulties, embarrassment arising from micrographia (for the paper survey), and the fatigue induced by the length of the questionnaire may explain the low completion rate of the last question among the patients with PD (Choi and Pak, 2005).

The fact that the survey could be completed either by patients or carers is not free of limitations. In healthcare surveys, there is the tendency carers to complete the questionnaires of more disabled patients, if this is permitted (Moule and Goodman, 2009). In addition, in the current survey, the carers responded to the items of the questionnaire based on their own perspective, which may have been different from that of patients. As the conduction of the present survey aimed to design a group-based therapeutic exercise and educational programme, based on the most prevalent responses; the findings may have deviated, if only patients with PD completed the questionnaire, because they may

have been less disabled than those who have had the questionnaire completed by their carers. This is of particular interest, as PD patients with severe clinically disability (four to five H&Y stages) and factors that restricted their participation in the exercise programme (e.g. dementia) were excluded from the RCT (sections 8.5.2 and 8.5.3). However, the survey's analysis did not explore whether there were any systematic differences in the responses that patients and carers gave. As this was not one of the study's objective, there was not probably sufficient statistical power to perform a sub-group analysis.

Lastly, the qualitative analysis, which was used for the last question, has received criticism, due to the challenges it faces compared to the quantitative analysis. Despite the fact that qualitative analysis is recommended for the detection and interpretation of personal beliefs, thoughts and ideas; all qualitative approaches lack the scientific credibility associated with traditionally accepted quantitative methods. Human mistakes are more common in qualitative studies, arising by errors in the understanding of the text and researcher bias. In particular, misrepresentations are possible when the respondents are unable to express themselves in the writing text; whereas researcher bias may be developed by the limited experience and viewpoints of researcher (Bengtsson, 2016).

### **7.5. Proposals for future studies**

The results and limitations of the present study should be taken into account for the implementation of future studies. Firstly, there is need for a large, nationwide, representative study to detect the sociodemographic characteristics, the restrictions in daily life and emotional well-being, and beliefs in PD population in Greece. Apart from the HPDA; potential respondents could be recruited from the Northern Greece Parkinson's Disease Association, neurologists, clinics and hospitals from all the regional units of the country. This procedure may assist to reach PD sufferers, ethnic minorities and immigrants living in the whole country.

Special emphasis should be given in the design of the questionnaire. A shorter questionnaire may increase the response rates; whereas the consultation of patients for the construction of the instrument will be important for the selection of the most relevant items. In addition, future studies, apart from the frequency, could assess the severity of restrictions in daily life, both during the on- and off-state of medication. As the complaints of patients related to disability tend to be more frequent and severe with the progression of the disease, future studies could investigate any changes as the disease progresses.

The descriptive design of the current study enabled the acquirement of many information, which may be useful for future research in this field. Future studies could explore in depth the relationships between some socio-demographic variables (e.g. age) and health status (e.g. severity of PD, years since PD diagnosis) with restrictions in daily life and mental health, which was beyond the aim of this survey. Regarding the marital status, it would be interesting to assess the quality of the relationship. For instance, whether patients in satisfying marriages experience less emotional disturbances than patients in troubles marriages. Lastly, future surveys with sufficient statistical power, completed either by patients with PD or carers, could explore possible differences in their answers, and how these could have implications on the results.

The plethora of motor restrictions, emotional disturbances, additional reported non-motor symptoms, ineffective antiparkinsonian medication, impacts –including falls and social impacts- and the negative beliefs and worries about the future of patients with PD in Greece (based on the findings of the present survey); indicate the need for the design of treatment strategies and care management beyond the control of motor symptomatology of the disease. Complementary treatments, such as therapeutic exercise, in conjunction with medication or multidisciplinary programmes may be effective to improve the motor and non-motor symptoms of the disease, and the QoL of patients and their carers. In Greece, the design of an evidence-based low-cost group therapeutic exercise programme, instead of individualised programmes, may be of particular importance for this purpose; due to the cuts in the public health services, including physiotherapy, and the reduced

income of residents. In addition special educational programmes could improve the patients' knowledge about PD and propose ways to overcome the daily difficulties arising from the symptoms of the disease. The need for the design of similar programmes in other countries is also supported by the findings of one study; where PD patients suggested programmes that include physical activity and education, which may help them to cope with the restrictions in emotional and motor domain due to PD (Uebelacker et al., 2014).

Lastly, in a time when more emphasis is placed on rehabilitation, such a tool –especially sections B to E- is probably needed to adequately assess the rehabilitation needs of those affected by PD and to evaluate the results of rehabilitation interventions. Measures of disability in ADLs and emotional well-being may be much more meaningful for the patient, and thus for clinical decision making, than traditional tools that are widely used by healthcare professionals (van Brakel et al., 2012).

## **7.6. Conclusions**

To our knowledge, this was a unique study, because it was the first that recorded the restrictions in ADLs and emotional disturbances due to PD, and the socio-demographic and health profile of patients with PD living in Greece. While an attempt was made to minimise bias and collect the most accurate data from respondents; there were several limitations, and the results should be interpreted with caution. The study revealed that the disease does not only affect physical function and patients' ability to have an active role in the society; but it also affects mental health and provokes negative thoughts, both for the patients and their carers. The reported daily challenges and emotional disturbances highlight the need to improve the provided services in this population; and they should be fully considered in the design of treatment strategies and care management, such as physiotherapy, which generally focus on controlling the motor symptoms of the disease. Thus, the most prevalent answers of the current survey were considered for the design of the community-based exercise and educational programme of the RCT.

### 7.7. Summary of Chapter 7

- The anthropometric characteristics (gender, age) of patients with PD living in Greece were in line with the results of previous studies.
- The ethnic background and place of residence of patients were not in accordance with the data of the Hellenic Statistical Authority for the overall population of the country, indicating coverage bias.
- The most prevalent reported motor disabilities revealed balance impairments and increased risk for falls.
- The patients may have not noticed respiratory impairments due to the restriction of their ADLs.
- Although only few patients stated anxiety and depressive disorders as comorbidities, the vast majority reported symptoms of anxiety and depression in a weekly basis.
- A direct comparison between the present and previous relevant studies was not feasible, due to limited provided data and differences in methodology.
- The results should be interpreted with caution due to several limitations; such as coverage bias, non-response bias and lack of statistical power.
- Despite the limitations, the results indicate the need for the design of treatment strategies and care management for the control of motor and non-motor symptomatology, and education of both patients with PD living in Greece and their carers about the disease.
- The most prevalent answers of the current survey were considered for the design of the community-based exercise and educational programme of the RCT.

# **CHAPTER 8**

## **RCT – METHODOLOGY**

## 8.1. Introduction

The present systematic review (Chapter four) revealed that the role of therapeutic exercise on depression in PD population, has received little attention; and it is not possible to draw firm conclusions about its effectiveness. To address this gap in the literature, the current RCT was designed; based on the Greek landscape, without the use of expensive and sophisticated equipment. The results of the present survey (Chapter seven) were considered for the design of an individualised and a group training protocol, and an educational programme by the author of the thesis. Some respondents of the survey also participated in the RCT, if the eligibility criteria were met. The steps as proposed by the (Consolidated Standards Of Reporting Trials) CONSORT statement were followed for reporting the present RCT (Moher et al., 2010).

## 8.2. Study aim, objectives and design

### 8.2.1. Aim of the study

The primary aim of the study was to develop and evaluate, over both the short and longer term, a community-based group exercise and educational programme to improve depressive levels in individuals with mild to moderate PD and comorbid depression. The subsidiary aim was to consider the effectiveness of this programme on anxiety levels, QoL, balance, FOF, functional mobility, walking endurance (exercise tolerance) and respiratory function.

### 8.2.2. Research questions

The research questions were formulated as follows:

1. *“What are the short and longer term effects of a community-based eight-week group exercise and educational programme in individuals with mild to moderate PD and comorbid depression; compared to controls who followed an unsupervised, individualised home-based exercise programme?”*



2. *“Is an eight-week community-based ‘group exercise and educational programme’ effective in improving the psychological and functional status, QoL and respiratory function of individuals with mild to moderate PD and comorbid depression?”*

### 8.2.3. Objectives of the study

The objectives of the study were:

1. To develop a community-based group and educational programme, and a booklet for unsupervised, individualised home-based exercise programme.
2. To study the relationships between the level of depression and anxiety; and several anthropometric characteristics, health status, and outcome measures of the study at: baseline; and at post-intervention and follow-up, if significant improvements in depressive and anxiety levels were detected.
3. To assess the effectiveness of a community-based group exercise and educational programme on psychological and functional (mobility) status, QoL, and respiratory function at post-intervention.
4. To determine whether the outcomes were maintained at the end of the three-month follow-up period.
5. To record the number and circumstances of falls and fall-related injuries during the whole study period, and identify the major predictors of falls.
6. To study the effectiveness of the community-based group exercise programme in terms of participants’ satisfaction, using a questionnaire survey.
7. To study the attendance with the group exercise and educational, and home-based exercise programme

### 8.2.4. Hypotheses

Based on the literature evidence, this study predicts better outcomes in the IG (community-based group exercise and educational programme) compared to the CG (unsupervised, individualised home-based exercise programme); and hence sets one-tailed hypothesis. The experimental (or alternative) hypothesis ( $H_a$ ) for this study was that the IG would receive a significant effect in any of the assessed outcomes over time, compared to the CG.

The corresponding null hypothesis (Ho) was that there would be no statistically significant differences in any of the assessed outcomes over time between the two study groups.

#### 8.2.5. Study design

This was an experimental study, as it dealt with the phenomenon of ‘cause and effect’ and the independent variables (intervention of the IG and CG) were manipulated to study their effects on the dependent variables (outcome measures) (Thomas et al., 2005). A parallel RCT was undertaken. The RCTs provide a high level of evidence, and low level of selection bias, due to randomisation. The parallel design facilitates the comparison between the study groups, to identify the superiority of an intervention (Evans, 2003).

The study included two groups: the IG and the CG. The participants of the IG received a community-based group exercise and educational programme of eight weeks ( $\approx$  2 months). In the same period, the members of the CG participated in an unsupervised, individualised home-based exercise programme. During the three-month ( $\approx$  13 weeks) follow-up period, all the participants followed an individualised home-based exercise programme. Three assessments were undertaken, as reported in section 8.6.1. The design of the RCT is represented in figure 8.1.

IG	O1	X1	O2	X2	O3
CG	O1	X2	O2	X2	O3

Abbreviations. CG: comparison group; IG: intervention group; O1: baseline assessment; O2: post-intervention assessment; O3: follow-up assessment; X1: ‘group exercise and educational’ intervention; X2: ‘individualised home-based exercise’ intervention.

**Figure 8.1.** Representation of the RCT design.

The current study was not blinded. In practice, it is difficult to blind therapists delivering the intervention or participants in rehabilitation studies (Wang and Bakhai, 2006). The

assessors of this study were also unblinded, because the chief investigator (PhD student) was the main assessor for the clinical tests. Furthermore, in trials in which key outcomes are self-reported, the assessor is considered to be blind only if the subject was blind to group allocation (Page, 2012a). In the current study, the questionnaires were completed by the participants.

### **8.3. Location and venues**

#### **8.3.1. Selection of regional unit in Greece**

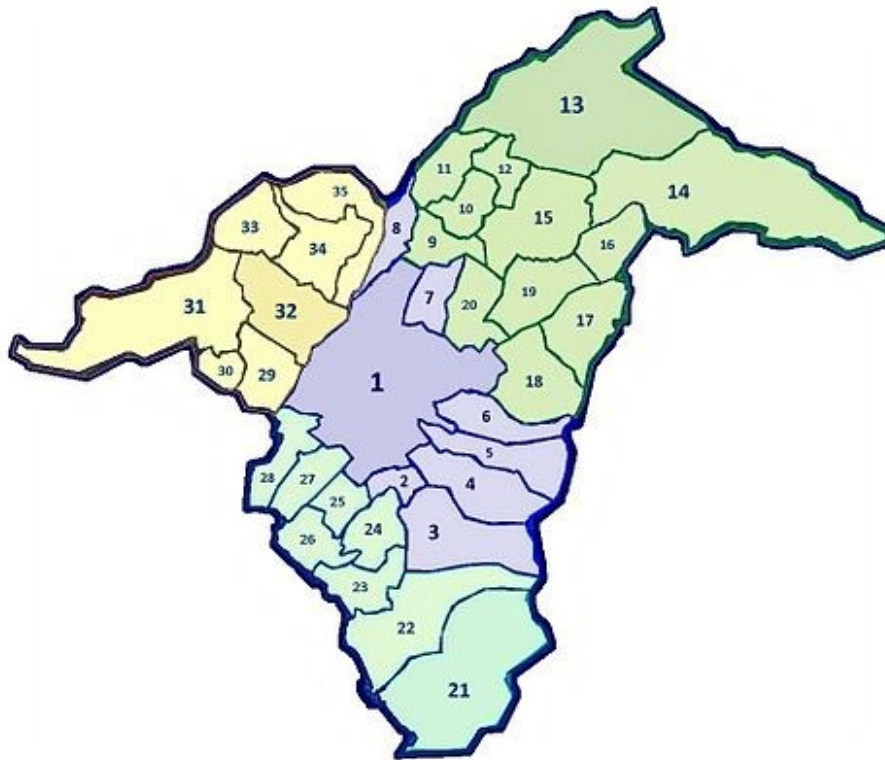
The researcher with the co-operation of the HPDA decided to conduct the study in Athens Metropolitan Area for several reasons. Firstly, as the 40% of the Greek population lives in Athens, it would be easier to recruit participants for the current study; and the total cost would be reduced compared with a study carried out in multiple cities. Athens also has the largest mass transit system of the country, giving the participants' access to the venues for the group exercise and educational programme, screening for inclusion and assessments. Furthermore, the HPDA could not offer volunteers for the research team to other regional units of the country, apart from Attica. Lastly, in Athens there are many facilities to conduct the study; such as hospitals and universities.

#### **8.3.2. Identifying venues**

The next step was to identify venues in Athens Metropolitan Area. The researcher, with the guidance of the HPDA, asked for permission to conduct the study in four public hospitals (251 Aviation General Hospital, 401 General Military Hospital, General Hospital 'Evangelismos' and University Hospital 'Attikon') between October 2013 and February 2014. Three hospitals (401 General Military Hospital, General Hospital 'Evangelismos' and University Hospital 'Attikon') denied immediately access to their facilities, due to logistical reasons. An Ethics Application Form was submitted only to the 251 Aviation General Hospital in October 2013. However, two months later (December 2013) the Rehabilitation Department of the hospital rejected the application for logistical reasons.

The plan B was to use public venues, which were offered to the HPDA by eight municipalities of Athens Metropolitan Area, to provide free services to patients with PD and their caregivers, since September 2014. Firstly, the availability of these venues was checked for the total length of the study. Secondly, the venues were screened by the researcher in November 2014, to ensure they met all the required features for the participants' safety, and performance of the exercises, as described in the training protocol (section 8.8) (Keus et al., 2004); and all the criteria of the Article 4 (Law 2725/1999) of the 'Hellenic General Specifications for the authorisation of a fitness centre' (Appendix 8.1) (Government Newspaper of the Hellenic Republic, 2006). Thirdly, additional issues, based on the experience and knowledge of the chief investigator were examined: free parking facilities around the buildings, suitable access to the buildings and venues for disabled individuals (e.g. special ramps in case of stairs, elevator), safe access to the toilets. venues equipped with air condition and heating system, without furniture or equipment that could minimise the provided exercise surface, and at least seven stable chairs into the venue with a stable back-rest -without armrests and casters- to perform the group training.

Based on the above criteria, the facilities in three municipalities (Athens, Piraeus, Filadelfia-Nea Halkidona) were declined. Hence, it was decided to conduct the study in five municipalities (Argyroupoli-Elliniko, Galatsi, Ilioupoli, Paleo Faliro and Peristeri), which met the standards to conduct the training and the assessments. The municipalities covered the south (Argyroupoli-Elliniko, Ilioupoli and Paleo-Faliro), central (Galatsi), and west (Peristeri) sections of Athens Urban Area. The geographical location of the selected municipalities on the map of Athens Urban Area is presented on image 8.1 (p. 141), whereas the addresses of the venues in table 8.1 (p. 141).



**Image 8.1.** Geographical location of the selected municipalities in Athens Urban Area (1 is the Municipality of Athens). 3: Ilioupoli; 7: Galatsi; 22: Argyroupoli-Elliniko; 26: Paleo Faliro; 32: Peristeri (adopted from Wikipedia).

**Table 8.1.** The addresses of venues where the study was conducted.

Municipality	Building	Address	Venue	Floor
Argyroupoli-Elliniko	1 <sup>st</sup> KAPI of Argyroupoli	27 Alexioupoleos Str, Argyroupoli, PC 164 52	Physiotherapy gym class	1 <sup>st</sup> floor
Galatsi	1 <sup>st</sup> KAPI of Gaslatsi	20 Orfeos Str, Galatsi, PC 111 46	Physiotherapy gym class	1 <sup>st</sup> floor
Ilioupoli	Town Hall of Ilioupoli	114 Sofokli Venizelou Av., Ilioupoli, PC 163 42	Ex- immigrant hall	Ground floor
Paleo Faliro	1 <sup>st</sup> KAPI of Paleo Faliro	43Pandrosou Str, Paleo Faliro, PC 175 64	Physiotherapy gym class	Ground floor
Peristeri	KYVE of Peristeri	1 Ethnarhou Makariou Av., Peristeri, PC 121 31	Ex- municipal health centre	Ground floor

Acronyms. KAPI: Open Protection Centres for the Elderly; KYVE: Municipal Conference and Multi-Venue Centre; PC: postal code.

### 8.3.3. Environmental conditions

During the exercise and the assessments, the environmental conditions (humidity and air temperature range) were kept stable. The training in PD population should be avoided in extreme temperatures (Gallo and Garber, 2011). Exercise in warm weather may cause exhaustion, due to dehydration and increased body's temperature; whereas exercise in cold weather may increase muscle tone and exacerbate the motor symptoms, as a response of hypothalamus to produce more heat and increase metabolism (LeMura and Von Duvillard, 2004; Sakellari et al., 2005). As the search of the literature did not reveal more specific recommendations for PD, the recommendations by Kleisouras (1997) for adults were followed. A temperature and humidity metre (A-10T UNI-T) ensured that the humidity levels were kept between 40% and 60%; and air temperature between 20 and 24 Celsius degrees (Kleisouras, 1997).

## **8.4. The research team**

### 8.4.1. Members and responsibilities

The main team consisted of 17 professionals: the chief investigator (PhD student) and 16 volunteers. Their responsibilities during the study are presented in table 8.2 (p. 143). The chief investigator was the coordinator of the whole study. In January 2015, the assistant physiotherapists were recruited from 'Parkinson Care', a company of primary health care for patients with PD based on Athens (Section 5.8.1); whereas the rest volunteers from the HPDA or social networks. The assistant physiotherapists were employees of 'Parkinson Care' and members of the 'Panhellenic Physical Therapy Association', in order to have the right to provide physiotherapy services. The chief investigator had some experience in exercise classes and previous teaching experience, and all the members of the research team (apart from the translator) had experience working with PD population. Lastly, the educational programme was conducted by a team of multidisciplinary professionals having previous lecturing experience in symposiums for PD population.

**Table 8.2.** Members of the research team and study's responsibilities

Profession	Study's responsibilities	Number of volunteers	Source of recruitment
Chief Investigator (PhD student)	Design of the intervention, delivery of brochures and posters, screening for inclusion, participants' assessments, instructor of the group exercise programme, educational programme (lecturer), data analysis	1	None
Assistant physiotherapists	Screening for inclusion, participants' assessments, assistance to the group exercise *	6	PC
Nurse	Delivery of brochures and posters	1	HPDA
Secretary, psychologist	PD patients' record, participants' randomisation and contact	2	
Neurologist	Screening for inclusion, educational programme (lecturer)	1	
Dietician	Educational programme (lecturer)	1	
Psychologist	Educational programme (lecturer)	1	
Physiotherapists	Advice for the selection of exercises	2	
Physiotheapist	Qualitative analysis	1	Social networks
Translator	Translation of completed FQs and SQs form Greek to English	1	

\* one of the assistant physiotherapists also participated in the pilot work

Acronyms. HPDA: Hellenic Parkinson's disease Association; FQs: Falls Questionnaires; PC: Parkinson Care; PD: Parkinson's disease; SQ: Satisfaction Questionnaires.

#### 8.4.2. Training of volunteers

A meeting was performed with the professionals involved in the RCT, to inform them about the aims of the study and their responsibilities. The SOP for the study was sent to them by e-mail, providing information for the study's methodology. Two additional 90-minute training sessions were conducted with the assistant physiotherapists, to improve their knowledge on the outcome measures, and the community exercise in PD. Training also involved formal practice and discussion; and hard copies of the grouped training protocol, participants' booklets and assessment forms were given to them.

## 8.5. Participants

### 8.5.1. Recruitment of participants

The subjects were recruited from the HPDA, and the municipalities where the study was undertaken, through the ways proposed by Berger et al. (2009) (internet, printed announcements, media). Specifically, the HPDA sent a newsletter via e-mail to its enrolled members, in February 2015, to inform them about the study. In addition, relevant monthly announcements were posted on the official HPDA website and facebook page from February 2015 to May 2015. In order to reach PD patients that were not enrolled with the HPDA, brochures (appendix 8.2) and posters (appendix 8.3) were delivered to some public buildings and local pharmacies of the municipalities where the study was conducted, between February and March 2015. Both the posters and brochures aimed to inform PD patients about the free services offered by the HPDA to the municipalities, and hence, about the current study. Lastly, a relevant advertisement (poster- appendix 8.3) was included in the local newspaper of the municipality of Peristeri.

The PD individuals who expressed interest in participating in the study had to contact via telephone, and enroll with the HPDA, if they were not already enrolled members. The study's aim was explained to them; basic demographic and PD-related characteristics (i.e. name, municipality of residence, confirmed PD diagnosis), contact details, and their municipality of preference for the study were recorded.

### 8.5.2 Inclusion criteria

The inclusion criteria were as follows:

1. Confirmed diagnosis of idiopathic PD as defined by the UK PDS Brain Bank criteria (NICE, 2006).
2. Both male and female population, because PD affects both genders (Ahlskog, 2009); members of the HPDA.
3. PD patients with mild to moderate clinical disability level (one to three H&Y stages), with or without walking aid. This criterion ensured that the participants would be able



to complete safely the proposed exercise programme, reducing the risk of falls and fall-related injuries (Keus et al., 2004).

4. Score of at least 24 on the Mini-Mental State Examination (MMSE), which guarantees adequate cognitive ability of individuals to participate in the exercise programme, and complete self-report questionnaires (Folstein et al., 1975).
5. PD patients with comorbid depression; a score at least eight as measured by the Hospital Anxiety and Depression Rating Scale- Depression (HADS-D) (Bjelland et al., 2002).
6. Stable dose of antiparkinsonian medication at least four weeks prior the start of the programme, and up to the end of the study. Dose and type of medication should remain the same in order to minimise its effects on the study's results (Hackney and Earhart, 2010).
7. Patients under antidepressant medication or not. The antidepressant medication should have started at least five weeks prior the start of the study, as it usually takes three to four weeks to respond to the treatment (Harmer et al., 2009); and the medication must have been kept at the same dosage through the entire study's period.
8. Patients available for the entire period of the study.
9. Ability to read, write, understand instructions and follow commands in Greek.
10. No previous participation in a therapeutic exercise training programme for PD and/or depression, to avoid prior training effect (Shulman et al., 2013).

### 8.5.3. Exclusion criteria

Individuals were excluded if:

1. They suffered from secondary PD, or received neurosurgery for PD—such as DBS—, to maintain the internal validity of the study with a more homogenous sample.
2. They had visual or hearing deficits that would eliminate their participation to the study.
3. They were receiving adjunct treatment for depression, such as CBT, as it would be unclear what intervention had an effect on the patient.
4. They suffered from an acute illness or chronic disorder, or received drugs, which could interfere with their safety during testing or training procedures or restrict exercise (Frontera et al., 2006).

#### 8.5.4. Sample size determination

Although the current project was a Phase I study, which does not require any sample size calculation (Charan and Biswas, 2013), the sample size was determined by the equation proposed by Noordzij et al. (2010) for RCTs in healthcare:

$$n = 2 [(\alpha + b)^2 \sigma^2] / (\mu_1 - \mu_2),$$

where 'n' is the sample size in each of the groups, 'α' the conventional multiplier for alpha level of significance 0.05 (5%), 'b' the conventional multiplier for statistical power 0.80 (80%), 'σ' the population variance (SD), and 'μ<sub>1</sub> – μ<sub>2</sub>' the difference the investigator wishes to detect between the study groups (absolute effect size). The power should be a minimum of 80% and the significance level not greater than 5% (Hicks, 2009). When alpha is chosen at 0.05 (5%), the value should be entered in the formula for 'α' is 1.96. Similarly, when power is chosen at 0.80 (80%), the value should be entered in the formula for 'b' is 0.8416 (Noordzij et al., 2010). Previous trials with therapeutic exercise in chronic diseases, where the HADS-D was the primary outcome measure, suggest that the data would be distributed with a SD of 2.7 (Bateman et al., 2001; Ridsdale et al., 2004; Arnardottir et al., 2006; Aydin et al., 2008; Bircan et al., 2008; Brittle et al., 2009; Jolly et al., 2009; Chien et al., 2011; Mitgaard et al., 2011; Murtenazi et al., 2011; Tsuchihashi-Mataya et al., 2013). For the current study, the researcher considered a difference in HADS-D of 4 between the study groups (μ<sub>1</sub> – μ<sub>2</sub>) as clinically relevant (Wang et al., 2009). Thus, entering the values in the formula, 28 patients per group were needed to answer the research question. As the researcher anticipated a 20% drop-out rate (Hicks, 2009), the initial sample should be 35 individuals per group. As the study had two equal groups (Noordzij et al., 2010), 70 PD patients were required.

#### 8.5.5. Screening for inclusion

One week before the screening for inclusion, the potential participants (n= 169) were informed by the volunteers (secretary, psychologist) about their meeting with the research

team. They were asked over the phone, if they were available for the whole study period, their transport options at the selected venues, their current mobility level (e.g. walking aid, wheelchair), and if they suffered from dementia. These questions provided a first screening. People unable to commit to the study or who were more disabled than the inclusion criteria, were not invited to the main screening assessment to the selected venues. At this stage, 18 patients with PD were not invited for screening: seven had severe mobility restrictions, two were not available for the total study period, two expressed transportation difficulties, three expressed no interest to participate in the study, and the telephone communication was not possible with four individuals. Hence, 151 potential participants were invited for screening. For this purpose, they were required to bring a confirmed diagnosis of PD, their national health booklet, the medicines they received, a pair of glasses, and their walking aid (if any); and get dressed in sportswear. Lastly, they were asked if they had any further questions relevant to the current study.

The screening for assessment was done by three healthcare professionals: the chief investigator, the neurologist and an assistant physiotherapist. The following tools were used for this purpose: the United Kingdom Parkinson's disease Society (UK PDS) Brain Bank Criteria (Marsili et al., 2018), Unified Parkinson's Disease Rating Scale (UPDRS) (Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, 2003), modified H&Y scale (Hoehn and Yahr, 1967), Schwab and England Activities of Daily Living (SEADL) scale (Sampaio et al., 2012), MMSE (Folstein et al., 1975), general health questionnaire (GHQ), Snijders and Bloem FOG Test (Snijders et al., 2012), and Hospital Anxiety and Depression Rating Scale (HADS) (Zigmond and Snaith, 1983) (sections 8.7.1-8.7.8).

Concerning the screening procedure, firstly, the assistant physiotherapist completed the MMSE. Secondly, the HADS was completed by the patient and returned to the assistant physiotherapist. The MMSE and HADS-D scores were calculated immediately. Then, the neurologist confirmed the PD diagnosis using the UK PDS Brain Bank criteria; and completed the UPDRS, modified H&Y scale, and SEADL scale. Lastly, the potential participants who met the criteria for PD were sent to the chief investigator. The GHQ was

completed and the Snijders and Bloem FOG test was performed. At the end of the day, the chief investigator and the neurologist read carefully the GHQ, and decided whether the individuals met the study's eligibility criteria. In case of doubt for their health, a medical clearance was requested ensuring them to participate in the study. Following screening, 70 individuals were eligible to take part in the study, and 81 were excluded. The reasons of exclusion are presented in table 8.3.

**Table 8.3.** Reasons of exclusion during the screening procedure.

Reason of exclusion	Number of excluded individuals (n= 81)
HADS-D score < 8	38
MMSE score < 24	9
Essential (idiopathic) tremor	5
DBS surgery	4
Not present in the screening assessment	3
Not able to attend the hours and days of the IG	3
Refuse to participate	3
No availability for the whole study period	3
Not stable PD medication	3
Severe low back pain	2
Knee inflammation	2
Transportation difficulties	1
4 H&Y stage	1
Recent bypass surgery	1
Recent stroke	1
Severe COPD	1
Diplopia (double-vision)	1

Acronyms. COPD: chronic obstructive pulmonary disease; DBS: deep brain stimulation; H&Y: Hoehn and Yahr; HADS-D: Hospital and Anxiety Rating Scale-depression subscale; IG: intervention group; MMSE: Mini Mental State Examination; PD: Parkinson's disease

#### 8.5.6. Consent form

Before the main assessment for screening, the assistant physiotherapist informed once more the potential participants about the study and its aims, and answered promptly and honestly any relevant questions. The 'Participant Information Sheet' (Appendix 8.4-8.5) and the 'Informed Consent Form' (Appendix 8.6-8.7) were given to them. They were

requested to read carefully the 'Participant Information Sheet'. This procedure ensured that the subjects had an adequate understanding of the research study nature, purpose and implications (Sim and Wright, 2000). The people who met the eligibility criteria and wanted to participate in the study, had to bring the signed form to the first session of the baseline assessment. Hence, they had at least three working days to decide about their participation in the study.

#### 8.5.7. Randomisation procedure

Once the screening procedure was completed, the randomisation was performed by a volunteer (psychologist), in order to give each subject an equal chance of being in either the IG or the CG (Sim and Wright, 2000). The random allocation was achieved with a computer programme through the website [www.randomization.com](http://www.randomization.com), which is very simple and easy to implement (Suresh, 2011) in 1:1 ratio. Five randomisation procedures were performed, one for each municipality. Firstly, on a blank paper the names of participants were written alphabetically (by surname). At the left of each name, there was written an increasing Arabic number for each participant. Then, the third generator of the software was selected for the randomization, because it generates a random permutation of integers, and it is particularly useful for selecting a sample without replacement. The software randomly provided two equal columns with Arabic numbers corresponding to participants' names. The first column was for the IG, and the second for the CG.

The allocation was concealed, because the volunteer, who performed the randomisation procedure, was not involved in the 'exercise and educational' programme or the assessments. The members of the research team, who participated in these fields, were unaware about the randomisation process. The randomisation assignments were kept in opaque, sealed envelopes and unsealed by the researcher after the end of pre-intervention assessment. Similarly, the participants were informed of their allocation in telephone contact by the two volunteers (secretary, psychologist) before the commencement of the intervention, after the end of the baseline assessment.

#### 8.5.8. Meeting with the participants

Once the baseline assessment was completed and the subjects were informed of their allocation to the study groups, two one-hour meetings were held in the study venue of each municipality: one for the IG, and one for the CG. The subjects were informed about the time and date of their group meeting by telephone by the professional volunteers. The members of the IG were provided with the 'Group exercise booklet' (section 7.10.1), and the CG with the 'Individualised home-based exercise booklet' (section 7.10.2). The chief investigator explained how to complete the walking diary, falls diary (FD) and falls questionnaire (FQ); and perform the home-based individualised exercise. They were also asked to bring back the completed booklets at the post-intervention assessment. Lastly, it was explained to the members of the CG that if the results of the IG would be significant, the same group exercise and educational programme would be offered to them, after the data analysis. This may minimise the drop-out rate in the CG (Berger et al., 2009).

### **8.6. Assessment protocol**

#### 8.6.1. Introduction to the assessment protocol

Three assessments were undertaken: the pre-intervention (baseline) assessment, prior the start of the intervention, to ensure that the baseline characteristics between the study groups were similar; the post-intervention assessment, at the end of the eight-week intervention period, to determine the short-term effectiveness of the intervention; and the follow-up assessment, three months after the end of the intervention, to record the longer term effectiveness of the programme. A three-month follow-up period was selected, because evidence suggests that short exercise programmes in PD (lasting from four to 12 weeks) have beneficial effects on mobility, which continue for at least three months after the treatment completion (Mak et al., 2017). However, the systematic review of this thesis (Chapter 4) did not reveal any relevant data for depression in PD.

The outcome measures of the present RCT, what they measure, and the objective of the study they are related are presented in table 8.4 (p. 151). The rationale for the selection of

these tools is analysed in section 8.7. The ‘Satisfaction Questionnaire’ (SQ) was given only to the members of the IG at the end of the intervention period. The HADS-D was the primary outcome measure of effectiveness, whereas the rest tools were the secondary outcome measures of the study.

**Table 8.4.** Measurement tools, what they measure and related study’s objectives.

Measurement tool	What it measures	Objectives of the study
Hospital Anxiety and Depression Scale- Depression (HADS-D) subscale	Depression levels	2, 3, 4
Hospital Anxiety and Depression Scale- Anxiety (HADS-A) subscale	Anxiety levels	2, 3, 4
Parkinson’s Disease Questionnaire 39 (PDQ-39)	Quality of life	2, 3, 4
Timed Up and Go (TUG) test	Functional mobility	2, 3, 4
Berg Balance Scale (BBS)	Balance	2, 3, 4
Falls Efficacy Scale International (FES-I)	Fear of falling	2, 3, 4
2-minute walk test (2MWT)	Gait endurance	2, 3, 4
Spirometry	Lung function	2, 3, 4
Falls diary (FD)	Number of falls	5
Falls questionnaire (FQ)	Circumstances of falls and fall-related injuries	5
Satisfaction questionnaire (SQ)	Participants’ satisfaction for the exercise and educational programme	6
Attendance form (AF)- group programme, Attendance form (AF)- individualised programme	Adherence to the programme	7

#### 8.6.2. Characteristics of the assessment protocol

The conditions during and between the assessments were stable in order to not influence the outcome (Keus et al., 2013). All the assessments were held in the selected venues of the municipalities; apart from the 2-minute walk test (2MWT), which was performed in a corridor of the buildings -where the assessment was performed-, due to its long walking path (12 metres). Both the temperature and the humidity levels remained stable, as described in section 8.3.3. In addition, the same equipment (e.g. chair) was used for all the

clinical tests. The participants were tested by the chief investigator and the assistant physiotherapists. All participants were given at least a five-minute recovery period between different clinical tests to decrease fatigue (Dibble et al., 2008). The majority of self-administrated tools [HADS, Parkinson's Disease Questionnaire 39 (PDQ-39), Falls Efficacy Scale International (FES-I)] were completed by the patients during the assessments; apart from the FD, FQ and SQ, which were completed at their homes. They were strongly encouraged to respond honestly to all the questions and seek clarification from the assistant physiotherapist if something was unclear. The completed questionnaires were collected by the assistant physiotherapist. The assistant physiotherapist also checked if all the items of the HADS, PDQ-39 and FES-I were fully completed and if only one answer was selected in each item. Lastly, the two attendance forms (AFs) (AF-group programme, AF-individualised programme) were completed by the chief investigator, secretary and psychologist.

Each assessment was completed in two sessions, lasting approximately 60 minutes each. Between the two sessions there was a break of one to two working days, based on the number of subjects in each municipality. The HADS, BBS, FES-I and TUG were completed in the first session; whereas the PDQ-39, 2MWT and spirometry in the second session. As some items in the PDQ-39 resemble items in the HADS, these questionnaires were not filled out in the same session; to avoid participants looking back at their previous responses, and to complete the questionnaires honestly (Marinus et al., 2002a). Regarding the baseline assessment, the HADS was completed during the screening assessment, which was held one week prior the baseline assessment; whereas the FD was completed in the second session. The SQ was completed voluntarily by the members of the IG, and submitted either in the first or second session of the post-intervention assessment.

All the assessments of each participant were carried out at similar times of the day and during the 'on-state' to minimise the effects of motor fluctuations, and for safety reasons (Keus et al., 2013). Thus, subjects were asked to take their L-dopa dose about one hour



prior the assessment to ensure that they were at their best 'on-state' (Protas et al., 2005). They were always dressed in sportswear to perform the clinical tests (Keus et al., 2013).

### 8.7. Screening and assessment tools

The selection of the screening and assessment tools was consistent with the aims and the objectives of the study. A systematic approach was followed to select the appropriate tools. The selection process included four steps. Firstly, disease-specific instruments were preferred instead of generic instruments, as they reflect better the special characteristics of the disease and the effectiveness of intervention (Guyatt et al., 1986). Although there are generic instruments 'recommended'<sup>18</sup> for PD population, they lack specificity, and they seem more helpful in studies including populations suffering from different diseases to allow comparisons (Martinez-Martin et al., 2011). Secondly, 'recommended' instead of 'suggested/reasonable'<sup>19</sup> tools were selected, based on the reports of the EPDA (Keus et al., 2013) and Parkinson Evidence Database to Guide Effectiveness (PEDGE) (Kegelmeyer et al., no date). Thirdly, the clinimetric properties –reliability, validity, responsiveness, sensitivity- of the measurement tools were examined, to select tools that meet the desired characteristics for the current study (Loretz, 2005). Lastly, as the project was conducted in Greece, the selected tools should have been translated in the Greek language, and their clinimetric properties should have been examined in the Greek population. Special attention was given to the visual appearance of the self-administrated scales, and the procedure that is described in the paper questionnaire of the survey (section 5.5.9) was followed to design the assessment forms.

The selected screening and assessment tools for the current study have been already reported in Sections 8.5.5 and 8.6.1 respectively. Only the HADS was used both as screening and assessment tool. Sections 8.7.1-8.7.17 provide evidence for the selection of these instruments.

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<sup>18</sup> Tools with high clinimetric properties and clinical utility, that have been used in clinical studies in PD population.

<sup>19</sup> Tools with reasonable clinimetric properties and clinical utility, that have been used in clinical studies in PD population.

### 8.7.1. Hospital anxiety and depression rating scale (HADS)

In the current study, the HADS was used as a screening tool for identifying depression and anxiety, and as assessment tool to evaluate the treatment response (Zigmond and Snaith, 1983). The description of the HADS, and the Greek and English version of the scale are presented in appendices 8.8-8.10.

#### *Rationale for screening depression*

Although a structured interview, based on the DSM or ICD criteria, is considered the gold standard for the diagnosis of mental disorders, this is not always practical (Jacob, 2006). The clinical interview may require a long time for the correct diagnosis, expert staff to administer the interview, and it may be expensive (Nordgaard et al., 2012). Thus, this plan was declined for the current study. The second option was the use of rating scales, completed either by the patient or by a clinician. Williams et al. (2012) stated that almost all the rating scales are appropriate tools to identify depression in PD, when an optimum cut-off score demonstrates high sensitivity and specificity. However both of them are not official diagnostic tools for depression, and they cannot replace the need for a clinical diagnosis (Jacob, 2006).

With respect to the clinician-rated scales, both the HAM-D and MADRS are recommended tools for identifying depression in PD and screening its severity (Nordgaard et al., 2012; Torbey et al., 2015). However, they should be administrated by experienced staff to complete the items through interviews, and their completion time is longer than the self-report rating scales (Schrag et al., 2007; Williams et al., 2012). Due to the inability to find relevant professionals, and the unawareness of the chief investigator to complete these clinician-rated scales, the HAM-D and MADRS were also declined. In addition, despite the fact that the literature search identified Greek versions of these scales; no study was found to examine their clinimetric properties. The 'mentation, behaviour and mood' part of the UPDRS assesses the general emotional well-being in PD. However, the UPDRS is not a recommended tool to diagnose depression or measure its severity; due to limited face,

content and construct validity, and test-retest reliability (Schrage et al., 2007; Torbey et al., 2015).

On the contrary, the self-report questionnaires do not require experienced staff and are completed by the patient (Schrage et al., 2007). Although many self-report scales have been validated in PD, few studies have assessed the comparative validity of rating scales in PD (Schrage et al., 2007; Williams et al., 2012; Torbey et al., 2015). The most common proposed scales for the detection of PD depression are: the Beck Depression Inventory (BDI), the Geriatric Depression Scale (GDS) (Williams et al., 2012; Torbey et al., 2015), and the Zung-Self Rating Depression Scale (SDS) (Schrage et al., 2007). These scales have strong psychometric properties for depression screening (Schrage et al., 2007; Williams et al., 2012), apart from the SDS, as further evidence is needed to establish its validity (Schrage et al., 2007). Although the GDS is suitable for senior PD population, further research is needed for younger patients (Schrage et al., 2007). Furthermore, only the short-form of the GDS has been translated and validated in the Greek language (Fountoulakis et al., 1999). Lastly, there are concerns about the number of somatic items that are included in the BDI and SDS, which may make difficult to differentiate between the depressive symptoms and the motor symptoms of PD, limiting their use as a screening tool for depression. (Schrage et al., 2007; Williams et al., 2012).

There is some evidence to support the use of the HADS to identify depression and measure its severity in the current study. Despite the fact that the HADS was originally designed to be used with hospital populations, it has been found to perform well with non-hospital groups (Snaith, 2003). Both the Hospital Anxiety and Depression Scale- Anxiety (HADS-A) and HADS-D subscales seem suitable for screening anxiety and depression in a non-psychiatric medical population, because they lack somatic items (Zigmond and Snaith, 1983). Thus, the HADS subscales could be used to monitor changes in PD anxiety and depression, irrespectively the progress and the severity of motor symptoms (Leentjens et al., 2008).

Although there is limited evidence so far, experimental studies support that the HADS-D has acceptable properties for detecting depression in: cardiac patients (Stafford et al., 2007); multiple sclerosis (Watson et al., 2014); and PD (Mondolo et al., 2006). The HADS-D subscale has also been found to assess well the severity of depression among healthy and non-healthy populations, such as diabetes and coronary heart disease (Bjelland et al., 2002). However, in PD-free population evidence suggests that the HADS-D is equal to Patient Health Questionnaire 9 (PHQ-9) to identify only mild and moderate depression, whereas the PHQ-9 seems superior to identify severe depression (Hansson et al., 2008). This may be linked to the fact that the HADS-D excludes most of the somatic symptoms, which may be present in severe depression (Schrage et al., 2007). As the majority of PD patients suffer from mild to moderate depression (Marsh, 2013), and the HADS has been translated and validated in the Greek language (Mystakidou et al., 2004; Michopoulos et al., 2007); it was decided to use just the HADS-D as an instrument for identifying and measuring the severity of depression in this study.

#### *Rationale for screening anxiety*

There are no 'recommended' anxiety scales for PD, but only 'suggested', as: basic information about validity and reliability in PD population is missing (Leentjens et al., 2011), they focus only on the symptoms of GAD and panic disorder, and they were not designed to identify specific anxiety disorders (Leentjens et al., 2008). However, the GAD is the most prevalent anxiety disorder in PD (Broen et al., 2016). The 'suggested' self-reported scales for anxiety in PD include: the BAI, State-Trait Anxiety Inventory (STAI), HADS-A subscale (Leentjens et al., 2008), Geriatrics Anxiety Inventory, and Parkinson Anxiety Scale (Leentjens et al., 2014). To our knowledge, only the STAI and the HADS-A have been translated and validated in the Greek language (Mystakidou et al., 2004; Fountoulakis et al., 2006; Mystakidou et al., 2009). Neither scale was found superior with respect to its validity and reliability (Leentjens et al., 2008). Between the 40-item STAI and seven-item HADS-A, the HADS-A was selected, because it is shorter and quicker to complete it.

*Clinimetric properties*

Meta-analytic evidence indicates that the HADS is a valid and reliable tool for screening anxiety and depression in the general population. The test-retest reliability of the whole scale is good to excellent, whereas the concurrent validity is satisfactory. The internal consistency of the HADS-A is excellent, and of the HADS-D varies from adequate to excellent (Herrmann, 1997; Bjelland et al., 2002). However, the face validity of both subscales is moderate (Leentjens et al., 2008; Torbey et al., 2015). This is related to the fact that the HADS-D does exclude some items of severe depression –having ceiling effects-, such as psychotic features and suicide thoughts. Thus, the HADS-D subscale may be non-sensitive for severe depression, but further research is needed (Torbey et al., 2015). Similarly, the items of the HADS-A do not reflect defined anxiety symptoms according to the DSM criteria (Leentjens et al., 2008).

Regarding PD, the scale is also valid, reliable and responsive for use in PD (Rodriguez-Biazquez et al., 2009). It appears to have good test-retest reliability, and satisfactory internal consistency (Leentjens et al., 2001; Marinus et al., 2002a; Rodriguez-Biazquez et al., 2009). The absence of any information about the criterion validity of the scale, keeps the HADS-A as a ‘suggested’ scale to screen anxiety in PD population. The two subscales (HADS-D, HADS-A) have no floor or ceiling effects (Marinus et al., 2002a; Rodrigues-Biazquez et al., 2009), except only one ceiling effect for item eight (‘slowing down’) (Rodrigues-Biazquez et al., 2009). This may be explained by the fact that this item overlaps major motor symptoms of PD (Schrag et al., 2007). The literature search did not reveal the minimal clinically important difference (MCID) for the HADS and its subscales in PD or other neurological disorders. However, the established MCID value for HADS-D and HADS-A in inpatient population with chronic obstructive pulmonary disease (COPD) is equal to 1.5 (Puhan et al., 2008).

*Strengths and limitations*

Apart from the data that were reported previously, the HADS and its subscales appear to have additional strengths and limitations. The HADS is a low-cost tool that captures

information on both depression and anxiety, whereas the majority of mood scales focus on one particular aspect of mood (Snaith, 2003). The results are easy to interpret with higher scores on each individual scale or the entire scale indicating greater anxiety, depression or general psychological distress (Johnston et al., 1995; Roberts et al., 2001). The completion time of the scale is short, varying from two to five minutes.

On the contrary, the HADS-D addresses less DSM criteria for depression than other rating scales, such as the HAM-D and the BDI (Shumway et al., 2004; Williams et al., 2012). The HADS-D emphasises in anhedonia<sup>20</sup> rather than sadness (Schrag et al., 2007), and some non-somatic symptoms (cognitive symptoms, guilty, suicidal thoughts) are not recorded. Regarding anxiety, the HADS-A was developed as a brief measure of generalised symptoms of anxiety and fear, and not for detecting specific anxiety disorders based on the DSM criteria (Leentjens et al., 2008). However, the study by Terluin et al. (2009) proposed cut-off points for GAD and panic disorder in a distressed population.

### *Cut-off points*

A score at least eight for either the HADS-A or HADS-D was suggested to indicate anxiety and depression; and at least 11 for the clinical anxiety and depression (Zigmond and Snaith, 1983). The review by Bjelland et al. (2002), based on the results of previous studies in somatic diseases with comorbid depression or anxiety, also suggests a cut-off score of eight for both subscales for optimal balance between sensitivity<sup>21</sup> and specificity<sup>22</sup> of about 0.80. Regarding PD, further research is needed for the best cut-off score distinguishing depressed and non-depressed patients (Torbey et al., 2015). Thus, in the current study, based on the suggestions of Bjelland et al. (2002) for chronic diseases, a cut-off of eight out of 21 in each subscale was selected.

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<sup>20</sup> Loss of pleasure, interest

<sup>21</sup> True positive rate

<sup>22</sup> True negative rate

*Greek version*

The Greek version of the HADS has not been validated in PD population yet. However, the administration of the scale to patients with advanced cancer and general hospital population (inpatients and outpatients), indicated adequate to high internal consistency, test-retest reliability and concurrent validity (Mystakidou et al., 2004; Michopoulos et al., 2007).

8.7.2. UK PDS Brain Bank criteria

Although the potential participants were required to provide written medical clearance from their neurologist to certify them as idiopathic PD sufferers; the neurologist examined the participants to ensure the disease. The examination was based on the UK PDS Brain Bank Criteria (Appendix 8.11). These are the most widely accepted clinical criteria for PD diagnosis (Massano and Bhatia, 2012), recommended by the National Institute for Clinical Excellence (NICE) guidelines (National Collaborating Centre for Chronic Conditions, 2006). The diagnostic accuracy rate using these criteria is 82.7% (Rizzo et al., 2016).

8.7.3. Unified Parkinson's Disease Rating Scale (UPDRS)

The UPDRS (officially known as UPDRS version 3.0) was used to assess the PD impairment and disability at baseline (Sampaio et al., 2012). It is a multidimensional instrument, and measures both the motor and non-motor features of the disease (Ebersbach et al., 2006). Although its reliability has been examined more than its validity, it is the 'gold standard' for the assessment of PD, and the most frequently applied instrument in clinical setting and research (Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, 2003; Ebersbach et al, 2006). It is also an easy-to-use instrument, its completion time is between 20 and 30 minutes, and the coverage of motor symptoms is comprehensive (Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, 2003).

On the contrary, the tool does not provide a sufficient measurement of some non-motor symptoms of PD (e.g. depression), whereas some prevalent non-motor symptoms -such as

anxiety, fatigue and sexual dysfunction- are not covered (Ebersbach et al., 2006). In addition, as the instructions for raters are inadequate, special training is needed (Goetz, 2006). Lastly, the Part IV of the scale has been criticised negatively. In particular, the five-point option of some items and the dichotomous rating of others, make the overall quantitative analysis difficult; because the first assess the severity of disability and the others are related with the presence or absence of some signs (Sampaio et al., 2012). Thus, a new advanced scale was developed in 2007 by the Movement Disorder Society (MDS), entitled MDS-UPDRS. The four parts of the MDS-UPDRS appear adequate to excellent internal consistency, and excellent concurrent validity, when compared to the UPDRS (Goetz et al., 2008).

Both versions of the UPDRS have been officially translated in the Greek language (International Parkinson and Movement Disorder Society, no date). However, there is no study that examined the validity and reliability of the Greek version so far. Between the two versions, the neurologist selected the UPDRS (version 3.0), as he was experienced and trained on this version of the scale. The UPDRS scale and its description are found in appendices 8.12 – 8.14.

#### 8.7.4. Modified Hoehn and Yahr (H&Y) Scale

The most widely and universally accepted staging system for overall functional disability in PD is the H&Y scale (original version) (Hoehn and Yahr, 1967), and its modified version, the Modified H&Y scale. The H&Y scale has been used extensively in many studies in PD population (Goetz et al, 2004), and it accompanies the UPDRS. It is a 'recommended' scale by the MDS Task Force on PD (Sampaio et al., 2012), and the PEDGE (Kegelmeyer et al., no date). The scale is simple and easily applied by specialists and non-specialists, and it is related to the whole disease spectrum (Goetz et al., 2004; Sampaio et al., 2012). However, the scale is limited by its focus on bilateral or unilateral involvement, and on balance impairments, whereas other motor or non-motor signs are unassessed. In addition, the categorisation relies highly on rater's subjectivity; without identifying the aetiology of impairment (Goetz et al., 2004).



With respect to the clinimetric properties of the scale, few studies have explored the clinimetric aspects of the H&Y scale, indicating high internal consistency and interrater reliability (Ginanneschi et al., 1988; Ginanneschi et al., 1991; Goetz et al., 2004); whereas no clinimetric data are available for the Modified H&Y scale (Goetz et al., 2004). Lastly, there is not official translation of any H&Y scale in the Greek language; however, they are found easily in the 'grey literature'. Between the two versions of the H&Y scale; the Modified H&Y scale was selected by the neurologist, as it has wider acceptance in Greece and it is used by him on a daily basis. The Modified H&Y scale and its description are found in appendices 8.15-8.17.

#### 8.7.5. Schwab and England Activities of Daily Living (SEADL) Scale

The SEADL scale, which accompanies the UPDRS (Sampaio et al., 2012), was used to assess the individual's ability to function in ADLs. It is a simple scale, quick to complete it, and no training is required for its administration (McRae et al., 2002). The SEADL scale has adequate test-retest reliability (Dal Bello-Haas et al., 2011), and interrater reliability between physicians, patients and caregivers (McRae et al., 2002). However, it does not examine the ADLs separately, and there may be some overlap, because the categories are broad (Shulman et al., 2010). Lastly, the scale is not validated in the Greek language. The SEADL scale and its description are found in appendices 8.18-8.20.

#### 8.7.6. Mini Mental State Examination (MMSE)

The MMSE was used to ensure that participants were of adequate cognitive function to participate in the study (Folstein et al., 1975). Although the Scale for Outcomes of PD-Cognition, and the PD-Cognitive Rating Scale are 'recommended' scales to assess cognitive impairment in PD (Kulisevsky and Pagonabarraga, 2009), no data concerning their translation in the Greek language were found. The Montreal Cognitive Assessment (MoCA) also seems sensitive instrument for this purpose (Hoops et al, 2009). However, its Greek version was validated, in general population and parkinsonian individuals with dementia, in 2016 (Konstantopoulos et al., 2016); after the completion of the current study.

The MMSE is considered the 'gold standard' screening instrument for the detection of cognitive impairment. It assesses the short-term memory (Sampaio et al., 2012), which is required for the participation in an exercise programme. Its clinical utility is good, because it does not require any special equipment or training for administration, and the completion time of the test is between five and ten minutes (Loue and Sajatovic, 2008). The Greek version of MMSE seems to be valid and reliable (Fountoulakis et al., 2000).

On the other side, the MMSE is less sensitive than MoCA for the detection of mild cognitive impairment in PD (Hoops et al., 2009). The MMSE also demonstrates floor effects in populations with severe cognitive impairment, and ceiling effects in populations with mild cognitive impairment (Wind et al., 1997). In addition, its score is not a diagnostic tool for dementia (Sampaio et al, 2012). The total score can be influenced by socio-demographic characteristics; such as age, and education level (Tombaugh and McIntyre, 1992). As the MMSE relies heavily on verbal response, reading and writing; patients with hearing and visual impairments, communication disorders, and low communication level on the test's language, may perform poorly (Wind et al., 1997).

The selected cut-off point for the current study was 23/24. Potential participants with score 23 or below were excluded. This was in accordance with the cut-off points proposed by Fountoulakis et al (2000) in Greek population, and with previous similar studies on therapeutic exercise in PD. The MMSE and its description are presented in appendices 8.21-8.23.

#### 8.7.7. General health questionnaire (GHQ)

The GHQ (Appendices 8.24 and 8.25), designed by the researcher, was a screening tool to identify whether the potential participants met the study's inclusion criteria; and if there were any additional contraindications or limitations for their participation in the study, apart from those that were detected using the UK PDS Brain Bank Criteria, MMSE, and HADS-D. In addition, basic anthropometric and socio-demographic data, and the health

status were recorded. The questionnaire was completed by the researcher by asking relevant questions; and by performing simple clinical examinations: measurement of height and weight, and calculation of the body mass index (BMI) (appendix 8.26). The parts of the GHQ are presented in table 8.5.

**Table 8.5.** The parts of the GHQ.

Parts of the questionnaire	Number of items
A. Background information	9
B. Anthropometric characteristics	6
C. Medical history of PD	10
D. Medical background	15
E. Family's medical history	6
F. Approval/refusal.	2

#### 8.7.8. Snijders and Bloem Freezing Of Gait (FOG) Test

In the current study, an instrument had to be selected to define freezer and non-freezer population, and assess the severity of FOG. The current 'gold standard' for clinical evaluation of FOG is the determination of the number of FOG episodes from video by independent raters (Morris et al., 2013). However, this method was rejected, because it is time consuming and costly. Although the self-administrated questionnaires that assess the severity and frequency of FOG episodes (Freezing of Gait Questionnaire and the New Freezing of Gait Questionnaire) are considered valid and reliable tools (Giladi et al., 2009; Nieuwboer et al., 2009), they do not utilise clinimetric tools to distinguish freezing and non-freezing population (Shine et al., 2012). In addition, they have not been translated in the Greek language so far. Hence, they were also rejected. The UPDRS scale contains one question about FOG (item 2.10) (Goetz et al., 2008); however, this instrument is not a validated methods to detect FOG (Sampaio et al., 2012).

The Snijders and Bloem FOG test is a clinical test, recommended by the EPDA (Keus et al., 2013), to detect freezers patients with PD. It is completed in a short time, usually less than ten minutes (Snijders et al., 2012). Turning around ‘on a spot’ appears to be the strongest provoking factor of FOG compared to other factors, such as walking through narrow passages (Snijders et al., 2008). According to the results of the study by Snijders et al. (2012), rapid full turns defined 84% of freezes in a subjective off period, before taking their medication; and rapid full turns dual task 96%. The specificity was significantly higher compared with other motor examinations such as half turns, wider turns and walking through narrow passages. It was hypothesised that narrow, high speed turns may provoke more often FOG, due to temporal and spatial conditions (Snijders et al., 2012). As a minority of PD patients appear FOG episodes during the ‘on-state’, it is recommended to perform the test during the ‘on-state’ and ‘off-state’ (Snijders et al., 2012). However, the test requires adequate clinical experience to distinguish differences between festination and FOG (Snijders et al., 2008).

Based on the above data, in the current study only the Snijders and Bloem FOG test was selected to detect freezing PD population, whereas the severity and frequency of FOG episode was not assessed. However, as the assessment took place only during the ‘on-state’; the test was not performed during the ‘off-state’. The description of the Snijders and Bloem FOG test and the relevant forms are in appendices 8.27-8.29.

#### 8.7.9. Parkinson’s Disease Questionnaire 39 (PDQ-39)

The ‘recommended’ PD specific instruments to assess QoL include: the Parkinson’s Impact Scale (PIMS), the Scales for Outcomes in Parkinson's Disease–Psychosocial (SCOPA-PS), the Parkinson’s Disease Quality of Life Questionnaire (PDQL), the PDQ-39, and the Parkinson’s Disease Questionnaire 8 (PDQ-8) (Marinus et al., 2002b; Martinez-Martin et al., 2011). However, the PIMS, SCOPA-PS and PDQL are not available in the Greek language; hence, they were rejected. Furthermore, the PIMS does not contain items on cardinal motor features, cognition and social stigma (Sampaio et al., 2012). The SCOPA-S is focused on psychosocial adjustment rather than in QoL, and lacks physical and mental health domains

(Martinez-Martin et al., 2011). The PDQL has a frame time of three months (Sampaio et al., 2012), which is not suitable for the current two-month intervention period; and is less precise than the PDQ-39 (Martinez-Martin et al., 2007).

Both the PDQ-8 and PDQ-39 have been translated and validated in the Greek language (Katsarou et al., 2001). Although the PDQ-8 (the short version of PDQ-39) has a very high correlation with the PDQ-39, it reaches lower reliability and validity than the PDQ-39 (Martinez-Martin et al., 2011). Therefore, the PDQ-39 was selected for the current study to assess the QoL. The description of the PDQ-39, and the Greek and English versions of the scale are provided in appendices 8.30-8.32.

The PDQ-39 is probably the most appropriate QoL instrument in PD, because its clinimetric properties are better than those of the previous reported scales, and it has been used in a large number of studies (Marinus et al., 2002b; Martinez-Martin et al., 2011). The English version of the scale demonstrated acceptable internal consistency and high test-retest reliability (Marinus et al., 2002b; Tan et al., 2004). In addition, the construct validity is well-established. The instrument appears to have no floor or ceiling effect (Marinus et al., 2002b). The calculated MCID value for the PDQ-39 summary index (SI) is 4.2 (Horvath et al., 2017). The PDQ-39 is also a low-cost tool, and its completion time is between 15 and 20 minutes (Keus et al., 2013). It does not need special training to calculate the total score and the score of each subscale; and it adequately covers physical, mental, and social domains (Martinez-Martin et al., 2011). The Greek version was found to have a high test-retest reliability, and internal consistency in patients with mild to moderate PD. The total score was also correlated well with the motor features of the disease and depression levels (Katsarou et al., 2001).

The PDQ-39 is not completely free of limitations. It assesses the frequency of some items, and not the impact or the intensity of the disease on patients' lives. As it assesses long periods of time (one month), a long-term memory is required (Martinez-Martin et al., 2011). The content validity is satisfactory, as it lacks items addressing some areas; such as

sleep, sexual function and transfers (Martinez-Martin et al., 2011). Lastly, the reliability of the social support subscale (test-retest and internal consistency) is inadequate (Marinus et al., 2002b).

#### 8.7.10. Berg Balance Scale (BBS)

The literature search identified two balance scales that are widely used in PD studies to assess balance: the Berg Balance Scale (BBS), and the Mini-Balance Evaluation Systems Test (Mini-BESTest). The Mini-BESTest assesses functional activities through different balance control systems, including dynamic gait. However, its clinimetric properties in PD population and the validation of the Greek version were established recently (Benka Wallen et al., 2016; Lampropoulou et al., 2016), after the completion of the current study. Thus, it was rejected, and the BBS was selected.

The BBS was developed to assess functional balance, without including walking activities (Berg, 1998); and it is reportedly used by the 71% of surveyed British neurorehabilitation physiotherapists (Yoward et al., 2008). Its clinical utility is high, because the test is simple and cheap to perform with minimal training required, and quick to complete it (15-20 minutes) (Berg et al., 1989). The EPDA proposes the BBS to assess stationary balance in PD patients (Keus et al., 2013). However, the PEDGE does only 'highly recommend' the instrument at H&Y stages two and three, as the functional balance is usually unaffected in the early stages of the disease (H&Y stage one) (Kegelmeyer et al., no date).

The clinimetric properties of the BBS are well established in PD population. Specifically, the scale appeared to have excellent test-retest reliability (Lim et al., 2005; Steffen and Seney, 2008), interrater reliability (Leddy et al., 2011), and internal consistency (Steffen and Seney, 2008). In addition, the criterion validity of the BBS is well established. There is excellent correlation with: the TUG test, and the UPDRS total score, indicating good validity for the disease severity (Kokko et al., 1997; Brusse et al., 2005). The Greek version of the scale in healthy older individuals appeared to have high internal consistency and interrater

reliability (Chatzitheodorou et al., 2006). The description of the BBS, and the Greek and English version of the scale are in appendices 8.33-8.35.

The reported limitations of the BBS in PD are related to the ceiling and floor effects (Leddy et al., 2011), the cut-off points, and the non-established MCID value in PD. The ceiling effects may arise, as the BBS does not assess dual task activities and freezing (however item 11 –turn 360°- may result in freezing) (Keus et al., 2013). Furthermore, patients in H&Y stage four are usually reliant on assistive devices, and so would likely exhibit floor effects (Leddy et al., 2011).

The cut-off points of the test usually indicate the risk of falling. Generally, a score of zero to 20 indicates a high risk of falling, 21 to 40 a medium risk, and 41 to 56 a low risk (Keus et al., 2013). In geriatric population, scores below 36 points are associated with at least one fall during the last six-month period (Shumway-Cook et al., 1997). However, the literature search did not identify any relevant study in PD population to discriminate fallers and non-fallers; but it seems that lower scores are associated with greater risk of falls (Dibble et al., 2008). Lastly, the MCID for improvement in balance, as measured by the BBS, was not found in patients with PD; but it is three points in inpatient and outpatient population suffering from multiple sclerosis (MS) (Gervasoni et al., 2017).

#### 8.7.11. Timed Up and Go (TUG) test

The EPDA recommends the TUG test and Modified Parkinson Activity Scale (M-PAS) as the most appropriate tools to assess functional mobility in PD. Although the M-PAS appears to have high clinimetric properties (Keus et al., 2009a); it was declined as there was no Greek version of the scale, and the required equipment (i.e. bed, pillow, sheet and blanket) was not available in the venues, where the assessment was performed. Thus, the TUG test was selected, which is recommended by the PEDGE at one to three H&Y stages (Kegelmeyer et al., no date). The description of the test and the completion forms are presented in appendices 8.36-8.38.

The TUG is a test, originally designed for use in the elderly population (Podsiadlo and Richardson, 1991). It is a measure of functional mobility to evaluate transfers, gait and dynamic balance, and to predict future falls (Keus et al., 2013). Thus, the test performance requires both muscle strength and balance. Subjects who are able to complete the test in less than 20 seconds, have been shown to be independent in ADLs and walk at speeds that are sufficient for community mobility. Those subjects requiring greater than 30 seconds to complete the test, tend to be more dependent in ADLs and often require gait aids (Podsiadlo and Richardson, 1991). Poor TUG performance (more time to complete the test) in PD has been associated with poor muscle strength, poor balance, slow gait speed, FOG and physical inactivity (Bennie et al., 2003). The test does not require special equipment, or a high level of assessor skill; it takes about five minutes to be performed (Podsiadlo and Richardson, 1991); and it is reportedly used by the 53% of the British physiotherapists working in the neurological field (Yoward et al., 2008).

The TUG test has reasonable psychometric properties in the general elderly population (Steffen and Seney, 2008), and in PD. With respect to PD, the test-retest reliability and interrater reliability during the 'on-state' and the 'off-state' were found high, even when the physiotherapy assessors had different levels of experience (Steffen and Seney, 2008; Huang et al., 2011). The significant correlation between the BBS and TUG test, supports the validity of TUG as a balance test (Bennie et al., 2003). Lastly, the TUG performance seems to be associated with previous falls in PD, and the test may distinguish PD population between fallers and non-fallers (Balash et al., 2005), using a cut-off score of 11.5 seconds (Nocera et al., 2013).

Nevertheless, it is doubtful whether the TUG test can predict future falls in general population. The reviews of Barry et al. (2014) and Schoene et al. (2013) concluded that although the TUG performance is associated with previous falls, the diagnostic accuracy of the TUG test to predict falls in the general population is limited. This may be explained by the fact that the cause of falls in elderly population is multifactorial. The TUG test reflects on strength and balance; and not on additional intrinsic and extrinsic factors that may be



associated with falling, such as poor vision, drugs taken (Rossat et al., 2010). Thus, cut-off points are not recommended to predict falls (Beauchet et al., 2011). Lastly, the author was not aware of the MCID value for the TUG in PD; however, Gautschi et al. (2017) found that it was 3.4 points in patients with degenerative disc disease.

#### 8.7.12. Falls Efficacy Scale International (FES-I)

FOF is a remarkably common fear in PD (Rahman et al., 2011). Due to the absence of specific-disease instruments to assess FOF in PD, a generic self-reported instrument was preferred for this purpose. The literature search identified six relevant scales: the Activities-specific Balance Confidence Scale (ABCS), Tinetti Falls Efficacy Scale (FES), FES-I, short version of FES-I, Survey of Activities and Fear of Falling in the Elderly (SAFFE), and mini SAFFE version (Sampaio et al., 2012). Although the FES is considered useful in assessing FOF in elderly communities, it seems to have ceiling effects in PD (Thomas et al., 2010). The comparison of test scales (FES-I, ABCS, SAFFE and mini SAFFE) assessing FOF in PD population, showed that all of them had high internal consistency and acceptable test-retest reliability. However, only the FES-I showed high test-retest reliability (Jonasson et al., 2014). Furthermore, to our knowledge, the FES-I and its short version are the only of the above FOF scales translated and validated in Greek population (Billis et al., 2011). In addition, the FES-I is the only FOF scale suggested by the EPDA in PD patients, and it allows a better insight understanding of the FOF than its short version (Keus et al., 2013). Thus, the FES-I was selected for the current study. The description of the scale, and the Greek and English version are in appendices 8.39-8.41.

The scale also is free of cost, easily completed in less than 15 minutes, and does not need any special training of assessors (Sampaio et al., 2012). A cut-off of 23 points discriminates between low and high fall concern (Delbaere et al., 2010). The Greek version showed excellent test-retest reliability and internal consistency, good discriminant validity, and no floor or ceiling effects in third age population (Billis et al., 2011). Although the study of Jonasson et al. (2014) verifies the high psychometric properties of the test in PD population, more research is needed to establish its validity and reliability. Thus, the EPDA mentions

that the test should be used and interpreted with caution, due to inadequate knowledge of its psychometric properties in PD population (Keus et al., 2013). Although, the MCID for the FES-I in PD was unknown, when the current RCT was conducted; the estimated value in geriatric population (70-90 years) is 3.5 seconds (Delbaere et al., 2010).

#### 8.7.13. Falls diary (FD) and Falls Questionnaire (FQ)

A FD (appendices 8.43-8.44) and a FQ (appendices 8.45-8.46) were used to record falls' number and their characteristics. These tools are advised by the EPDA, as they may provide physiotherapists with essential information about the frequency and circumstances of falling, and help them to set the goals for the design of the rehabilitation programme (Keus et al., 2013). The FD included a fall definition to facilitate its completion, adopted by the Prevention of Falls Network Europe: *"Fall is a sudden, unexpected event that results in coming to rest unintentionally on the ground or at some other lower level"* (Lamb et al., 2005: 1620). The FQ was a short, structured, self-completed instrument, designed by the researcher. Its design was based on previous relevant questionnaires in PD population (Keus et al., 2004; Morris et al., 2011; Keus et al., 2013). The questions were relevant to the falls' circumstances and their consequences. The estimated completion time of the FQ was between three and five minutes, based on the pilot study. The description for the completion of both instruments is in Appendix 8.42.

#### 8.7.14. Two Minute Walk Test (2MWT)

Exercise tolerance can be assessed by either maximal or submaximal exercise tests. In the current study, a submaximal test was preferred for the following reasons: the mean age of PD patients was over 60 years, fatigue is one of the most prevalent non-motor symptoms among PD population, and the ADLs are submaximal activities (Noonan and Dean, 2000). Furthermore, walking is one of the most common activities, which may be carried out by all ambulatory persons (Light et al., 1997). The 6 Minute Walk Test (6MWT) is a submaximal measurement of endurance, which assesses walking distance over six minutes (ATS, 2002). The test is the 'gold standard' to assess exercise tolerance in healthy populations and in

chronic diseases (ATS, 2002), and it is recommended by the EPDA in PD (Keus et al., 2013). Hence, the 6MWT was initially selected for the purpose of the current study.

Although the 6MWT was initially selected; after the end of the pilot study (section 8.12), it was decided to use an alternative submaximal walking test to assess the exercise tolerance. Furthermore, the performance of 6MWT in a single visit may exhaust the patients with PD, reducing their capacity for further evaluation during the same assessment session (Light et al., 1997). Thus, the 2MWT, a shorter version of the 6MWT, was selected. The 2MWT was firstly suggested in PD population by Light et al. (1997), and it is recommended by the PEDGE in PD patients with H&Y stage one to three (Kegelmeyer et al., no date). With minimal cost, training, and length of test (five minutes or less for one trial), the 2MWT is feasible in both research and clinical domains (Light et al., 1997). Although it is less used than the 6MWT, the literature search identified previous rehabilitation studies in PD (Ellis et al., 2008; White et al., 2009), which used the 2MWT to assess exercise tolerance.

The 2MWT has three major limitations: the psychometric properties of the test have not been examined in patients with PD; the normative values for the 2-minute walking distance (2MWD) are not well established, and the description of the test is not clearly reported.

Despite the fact that the 2MWT is a recommended test in PD (Kegelmeyer et al., no date); the psychometric properties of the test in PD have not been established so far. However, they are established in the healthy population and other neurological diseases; such as multiple sclerosis and stroke. The test is both valid and reliable in these populations (Kossak and Smith, 2005; Gijbels et al., 2010; Hiengkaew et al., 2012). The excellent correlation of distances covered in 2MWT and 6MWT, indicates high construct validity, and that the 2MWT is an alternative to the 6MWT as a measure of walking distance among patients with neuromuscular diseases (Gijbels et al., 2010). However, the systematic review by Pin (2014) concluded that more studies are needed to support that its validity and reliability. Concerning the MCID for the 2MWD, it was found 5.5. metres in people with COPD undergoing pulmonary rehabilitation (Johnston et al., 2017).

An additional limitation of the 2MWT is that the normative values for the 2MWD are not well established; and the available evidence is provided by the study of Bohannon et al. (2015) in an adult population (age: 18-85 years). Specifically, the 2MWD ranged from 64.6 to 300.8 metres, with a mean of 180.9 metres. The mean 2MWD was found 184.9 metres for men and 176 metres for women (Bohannon et al., 2015).

Lastly, there is not a standardised protocol for the 2MWT. However, previous experimental studies reported that they adopted the American Thoracic Society (ATS) guidelines for the 6MWT (ATS, 2002). Although Pin (2014) proposed a protocol for the test; this was not strictly followed the ATS guidelines for the 6MWT (ATS, 2002), as there was absence of verbal instructions during the test. The description of the protocol that was used in the current study, and all the relevant forms are presented in appendices 8.47-8.51.

#### 8.7.15. Spirometry

Spirometry is the 'gold standard' test, which was selected to evaluate the pulmonary function. Spirometry measures the volume of air that the patient is able to move from or to the lungs (Ranu et al., 2011; García-Río et al., 2013). As a 'gold standard' test, its clinimetric properties are well established (McCarthy et al., 1975). Despite the fact that the MCID values have not been calculated in PD yet, based on the literature search; the MCID values for the forced vital capacity (FVC) and forced expiratory volume in the first second (FEV<sub>1</sub>) are 3% in respiratory disorders (Kafaja et al., 2017) and 5% in COPD respectively (Jones et al., 2014). Apart from the diagnosis of respiratory diseases, spirometry is a valuable tool for the evaluation of rehabilitation programmes (García-Río et al., 2013). However, it is a valid tool only when used by trained staff (Burton et al., 2015). The chief investigator of the current study was trained, and had previous experience using the spirometre in a clinical setting. A hand-held spirometre (MIR Spirobank Usb) was selected, because it is portable. The standardisation guidelines of the ATS and the European Respiratory Society were followed (Miller et al, 2005; García-Río et al., 2013), as reported in Appendix 8.52.

#### 8.7.16. Satisfaction Questionnaire (SQ)

Patient satisfaction is an important and commonly used indicator for measuring the quality in health care; and it provides useful information for the improvement of healthcare services. (Prakash, 2010). Questionnaires that assess patients' satisfaction distinguish the treatment delivery and treatment effect (George and Hirsh, 2005). Thus, a SQ (Appendices 8.53-8.54), designed by the researcher, aimed to record the beliefs of the subjects about the group exercise programme, irrespectively from the outcome measures. The SQ was anonymous to let them express their beliefs openly; and its completion was optional, in order to avoid social desirable answers.

#### 8.7.17. Attendance forms (AFs)

Two AFs were designed to record the adherence of participants with the group-based exercise and educational programme (AF-group programme, Appendix 8.55) and the home-based individualised programme (AF-individualised programme, Appendix 8.56). The placing of a tick mark stated that the participant was present in each group-based exercise and educational class or followed the home-based individualised exercise programme on a weekly basis. The AF-group programme was being completed by the chief investigator, before the start of each group class; and the AF-individualised programme by the secretary, psychologist or chief investigator, through weekly telephone contact with each participant to confirm the adherence to the weekly home-based training programme.

### **8.8. Design of the group exercise programme**

#### 8.8.1. Parameters of the exercise programme

Special consideration was given by the author for the design of the exercise programme in order to capture the objectives of the study. Before the selection of specific exercises for the training protocol of the IG, basic features related to the training had to be defined. As the sample population was patients with PD suffering from depression, it was sensible to consider and combine the recommendations of organisations and results from previous effective studies in PD and depressed population, where possible. These features are

presented briefly in table 8.6. (p. 175), whereas the definition of some exercise terms are presented in the Glossary (p. xxix). The rationale behind the selected environmental conditions (temperature and humidity) is reported in section 8.3.3. With regards to outdoor exercise, the participants were advised to avoid exercise in extreme conditions (e.g. hot and cold weather, rainy days).

#### *Indoor versus outdoor exercise*

Although the EPDA proposes both indoors and outdoors exercise for PD population (Keus et al., 2013); the training was carried out indoors, apart from the aerobic exercise component, to ensure participants' safety and comfort. Indoors exercise also offers stable environmental conditions, eliminating the external factors that may affect the study's results (Hackney and Earhat, 2010). Moreover, there is limited evidence for outdoor training in PD and depression; even for outdoor walking, which is considered a promising effective approach in reducing depressive symptoms (Ranjbar et al., 2015). Lastly, the weather in Athens is unpredictable during winter, and dry and hot during summer.

#### *Group versus individual exercise*

A group exercise was preferred instead of individualised training. A group training protocol is recommended in PD populations with a disease severity from mild to moderate (1-3 H&Y stage) (Keus et al., 2007); to improve physical capacity, emotional well-being, and encourage socialisation (Keus et al., 2004). The social aspect may improve subjective feelings of well-being, and compliance with therapy might be increased (Ravenek and Schneider, 2009). Similarly, in a clinically depressed population, group exercise may improve depressive symptoms, due to peer support and encouragement (Rethorst et al., 2009). Although this was a research study and the participation was costless, group training is considered cheaper for the trainee compared to personal training (Porter, 2008).

**Table 8.6.** Parameters of the exercise programme.

Parameters	Parameters of the current study	Source(s) for the parameters
Indoor versus outdoor exercise	Indoor (the aerobic component –walking– was performed either indoors or outdoors)	Keus et al., 2013
Environmental conditions (for indoor exercise)	Humidity levels: 40%-60% ; air temperature: 20 <sup>0</sup> – 24 <sup>0</sup> C	Kleisouras, 1997
Group versus individual training	Group exercise (the aerobic training was individualised)	Keus et al., 2004; Keus et al., 2007; Ravenek and Schneider, 2009; Rethorst et al, 2009
Group size	5 to 6 participants	Allen et al., 2012
Supervised versus unsupervised training	Supervised (apart from the aerobic component -walking-)	Conn, 2010; Gallo and Garber, 2011; Allen et al., 2012; Stubbs et al., 2016
Instructions during exercise	As simple as possible	Keus et al., 2004
Total length of the exercise programme	8 weeks	Baatile et al., 2000; Scandalis et al., 2001; Protas et al, 2005; Cakit et al., 2007; Ravindran et al., 2009; Rethorst et al., 2009; Perraton et al., 2010; Smania et al., 2010; Keus et al., 2013; Volpe et al., 2014; Stubbs et al., 2016
Session duration	60 minutes (plus a 5-minute break)	Reuter and Engelhardt, 2002; Ravindran et al., 2009; Rethorst et al., 2009; Keus et al., 2013; Silveira et al., 2013
Exercise frequency	Twice a week (recommended frequency of aerobic exercise –walking–: 5 times a week)	Nelson et al., 2007; CPG, 2008; Gallo and Garber, 2011; Keus et al., 2013
Time of training	Morning or evening hours, during the ‘on’ phase of PD medication	Keus et al., 2013
Exercise intensity	Progressive, up to moderate	Craft and Perna, 2004; NHFA, 2007; Ravindran et al., 2009; Perraton et al., 2010; Gallo and Garber, 2011; Keus et al., 2013; Shu et al., 2014; Cruickshank et al., 2015
Exercise position	Sitting and standing	Keus et al., 2013
Types of exercise	ROM, respiratory, muscle strengthening, co-ordination, balance, gait, stretching and aerobic –walking–	Craft and Perna, 2004; Keus et al., 2007; Rethorst et al., 2009; Strohle, 2009; Gallo and Garber, 2011; Keus et al., 2013; King and Horak, 2009
Warm-up exercises	ROM and respiratory (diaphragmatic breathing) exercises	Sakellari et al., 2005; Goodwin et al., 2011; Volpe et al., 2014
Exercises of the dynamic phase	Respiratory (except diaphragmatic breathing), muscle strengthening, co-ordination, balance, gait exercises	Sakellari et al., 2005; Volpe et al., 2014
Cool-down exercises	Stretching	Hough et al., 2009; Goodwin et al., 2011; Page 2012b
Outdoor individualised exercise	Aerobic training (walking)	PSC, 2003; CPG, 2008; Robetson et al., 2012; Keus et al., 2013; Ranjbar et al., 2015

Abbreviations. ROM: range of movement.

*Group size*

Although the EPDA (Keus et al, 2013) advises a maximum number of eight patients per group; in the current study, each exercise group consisted of five to six individuals, because small training groups – up to six individuals- seem to improve the adherence of participants (Allen et al., 2012).

*Supervised versus unsupervised exercise*

A supervised, instead of an unsupervised, training was preferred; because reviews in PD concluded that exercise programmes under physiotherapist supervision were more effective at improving, mobility, psychological well-being and QoL compared with self-supervised home programmes (Conn, 2010; Allen et al., 2012). In addition, supervision may be necessary in patients with PD with more balance impairments (3-4 H&Y stage) (Gallo and Garber, 2011). Lastly, supervised training programmes are associated with high adherence and small percentages of drop-out in participants with mild to moderate PD (Allen et al., 2012), and mild to moderate depression (Stubbs et al., 2016). In the current study, each exercise class was supervised by the chief investigator and an assistant physiotherapist (section 8.4.1). Exercise classes were led by the principal investigator giving instructions to participants how to perform the exercises; whereas the assistant physiotherapist was present to provide technical and individual support to patients, when necessary, for the correct exercise performance.

*Instructions during exercise*

The instructions, which were given by the chief investigator, were as simple as possible. Further instructions during the performance of an activity or movement could lead to a dual task, which may affect balance and increase freezing episodes. Hence, there are more falls possibilities (Keus et al., 2004).



*Total length of the training period*

As a vulnerable group of patients who were also suffering with a co-morbidity participated in the study, it would be logical and ethical to keep the programme as short as has shown to improve both the primary and the secondary outcome measures. In PD, the EPDA recommends a treatment period of at least eight weeks to improve physical capacity (Keus et al., 2013). This length period is also supported by relevant experimental studies of medium to high quality to significantly improve: balance and FOF (Cakit et al., 2007; Volpe et al., 2014), muscle strength (Scandalis et al., 2001), cardiorespiratory fitness (Baatile et al., 2000; Volpe et al., 2014), functional mobility (Protas et al., 2005; Cakit et al., 2007), gait parameters (Protas et al., 2005; Volpe et al., 2014), QoL (Baatile et al., 2000; Volpe et al., 2014), and reduce the total number of falls (Protas et al., 2005; Volpe et al., 2014). Even a seven-week exercise programme was found effective in reducing depression symptoms in PD (Smania et al., 2010).

Regarding a depressed population, several lengths of exercise intervention have been shown to be effective in reducing depressive symptoms. The Canadian Network for Mood and Anxiety Treatments (CANMAT) recommends exercise programmes between eight and 20 weeks (Ravindran et al., 2009). One meta-analysis of RCTs showed that programmes with duration between four and nine weeks were more effective compared with interventions lasting 10 to 16 weeks; however, 18 of 20 studies with a duration up to nine weeks included just aerobic exercise (Rethorst et al., 2009). The review by Perraton et al. (2010) revealed that the majority of effective experimental studies in improving depression had a duration of eight weeks. Finally, long exercise programmes with a total length duration more than three months are associated with higher dropout rates than programmes of shorter duration (Stubbs et al., 2016). Based on the above information in PD and depression, it was decided that the total length of the exercise programme would be eight weeks.

*Session duration*

The session duration was approximately 60 minutes, plus a five-minute break for rest and socialisation. This was in accordance with the recommendations of the EPDA in mild to moderate PD (Keus et al., 2013), and CANMAT for clinical levels of depression (Ravindran et al., 2009). Furthermore, session durations over than one hour are not recommended in PD to avoid fatigue symptoms (Reuter and Engelhardt, 2002). Lastly, the meta-analyses by Rethorst et al. (2009) and Silveira et al. (2013) concluded that exercise bouts between 45 and 60 minutes are more effective in clinically depressed population, compared with sessions of longer or shorter duration.

*Exercise frequency*

The group exercise frequency was twice a week, plus 150 minutes walking a week (five times on a weekly basis). The weekly frequency was in accordance with the exercise recommendations, which propose therapeutic exercise at least twice a week in PD (Gallo and Garber, 2011; Keus et al., 2013), and in individuals with mild to moderate depression (CPG, 2008). In addition, with regard to the elderly population and patients with chronic diseases aged between 50 and 64 years, the American College of Sports Medicine and the American Heart Association (AHA) propose muscle-strengthening, stretching and balance exercise twice a week, whereas aerobic exercise five times on a weekly basis (Nelson et al., 2007). A low frequency of exercise (two to three times a week) is also associated with decreased dropout rates and increased adherence to the programme (Keus et al., 2013). There was a rest at least one day between the group exercise sessions, because the strengthening exercises should not include the same muscles on consecutive days; the muscles need a day to rest before training again (ACSM, 2009).

*Time of exercise*

Special attention was given to the training time; to perform the exercise during the 'on-state', when the parkinsonian symptoms are well controlled, and the individual's motor function is at its best (Keus et al., 2013). Although the EPDA advises that the patients should

take their L-dopa medication one hour before exercise (Keus et al., 2013), the time of receiving the antiparkinsonian medication may differ among the trainees of an exercise group. Thus, the potential participants during the screening assessment were informed about the exercise timetable in each municipality, and they were asked if during this period of the day were experiencing less parkinsonian kinetic symptoms. In addition, the exercise class was held at the same time each day -morning or evening hours- to avoid the diurnal fluctuations of the disease itself (Dereli and Yaliman, 2010).

### *Exercise intensity*

With respect to PD, the EPDA proposes either moderate [3.5-6 Metabolic Equivalent of Task (METs)] or vigorous activity (more than 6 METs) based on the fitness levels of each individual. Moderate activity is needed when walking on a flat surface (4.5-6.5 km/h) or doing general exercise at home; whereas vigorous intensity when doing jogging or participating in competitive sports, such as soccer. During moderate activities, individuals breathe harder than normal, and there is an increased heart rate; however they can carry out a conversation. In vigorous activities there is more increased heart and breath rate, and the normal conversation is difficult or not possible (Keus et al., 2013). The review by Shu et al. (2014) concluded that moderate intensity (50%-70%  $HR_{max}$ ) of aerobic exercise is effective in improving gait and cardiorespiratory parameters. Progressive anaerobic training with initial levels of 30-40% 1-repetition maximum (1-RM), being increased to 60% or 70% 1-RM, and from one to three sets of eight repetitions, seems to be effective in improving muscle strength (Cruickshank et al., 2015). Lastly, Gallo and Garber (2011) recommend a moderate intensity between 40% and 50% of 1-RM for depressed PD patients.

The CANMAT and the National Physical Guidelines for Australians recommend moderate intensity exercise in depressed population (NHFA, 2007; Ravindran et al., 2009). However, they do not define what moderate intensity is, and ways to measure it. Craft and Perna (2004) and Perraton et al. (2010) recommend a moderate intensity aerobic exercise (60% - 80% of  $HR_{max}$ ) to reduce levels of depression. A more dynamic intensity may be a deterrent

to continue the programme, and is associated with higher drop-out rate (Craft and Perna, 2004). Less evidence is available on anaerobic training in a depressed population. The high quality RCT of Singh et al. (2005) indicated that although both high (80% 1-RM) and low intensity (20% 1-RM) resistance training improved muscle strengthening, the results were greater in high intensity group.

In the current study, based on the above information in PD and depression, and having the knowledge that fatigue is a prevalent non-motor symptom of PD (Keus et al., 2013), and PD and depressed individuals are less physically active than their peers (NHFA, 2007; Keus 2013); it was decided to follow a progressive moderate intensity. As there was no available equipment to measure exercise intensity, a subjective scale was used for aerobic training (walking) (section 8.8.2), and patients were taught to recognise the signs to stop the exercise.

#### *Exercise position*

The exercises were performed in standing and sitting. The seated position was selected, because of the reduced danger of falling (Keus et al., 2013). During exercises in standing, to ensure safety, participants were required to stand behind the back of the chair (Sakellari et al., 2005). Although exercises in lying position are recommended in PD population (PAI, no date; PNZ, no date; Webber and Ramaswamy, no date; PSC, 2003; Cianci, 2014); they were not included in the present study, due to the shortage of beds and exercise mats.

#### *Types of exercise*

The selection of the types of exercise was related to the aims and objectives of the study. In patients with mild to moderate PD, the treatment goals of physiotherapy are: the prevention of inactivity, FOF and falls; and the preserving or improving physical capacity (Keus et al., 2007; King and Horak, 2009). Thus, an exercise programme may include aerobic, muscle strength, joint mobility, respiratory, balance and gait (Keus et al., 2007; Keus et al., 2013), and co-ordination exercises (Gallo and Garber, 2011). Although the

majority of previous experimental studies focused on the effectiveness of aerobic exercise in depression, it seems that both aerobic and anaerobic activities seem beneficial for the relief of mild to moderate depressive symptoms (Craft and Perna, 2004; Ströhle, 2009). Thus, Rethorst et al. (2009) supported that a regimen of aerobic and non-aerobic training may be more effective than aerobic exercise and resistance exercise itself. Hence, in this study a multimodal intervention was designed; including both aerobic and anaerobic types of exercise, which are listed as follows: ROM, respiratory, strengthening, co-ordination, balance, gait, stretching, and aerobic exercises.

#### *Parts of each exercise bout*

Each exercise bout consisted of three parts (Keus et al., 2013):

- A five to ten-minute warm-up period; including ROM exercises, plus deep diaphragmatic breathing (Goodwin et al., 2011; Volpe et al., 2014). The exercises were simple, involving only one part of the body; and in a seated position, due to the low risk for falls. Their low intensity aimed to prepare the musculoskeletal and cardiovascular system to respond better to the dynamic state of the rehabilitation programme (Sakellari et al., 2005).
- A 40 to 45-minute dynamic part, which involved more complex exercises of higher intensity: respiratory, strength, co-ordination, and balance and gait training (Sakellari et al., 2005; Volpe et al., 2014).
- A five to ten-minute cool down period, consisting of static stretches (Goodwin et al., 2011). The stretches were placed just in the cool-down period, as there is no evidence to support that stretches in warm-up prevent from muscle injuries; and static stretching as part of warm-up, is associated with reduced muscle strength (Page, 2012b), or with reduced performance in sports (Hough et al., 2009).

#### *Special exercise considerations in Parkinson's disease*

There are three exercise considerations for the design of an exercise programme in PD. Firstly, due to the imbalance between the agonist muscles that contribute to opening movements (i.e. extensors) and antagonist muscles that facilitate closing movements (i.e.

flexors) (Gallo and Garber, 2011); it is recommended to include a strong focus on strengthening on extended muscles of the body, and stretching on the shortened muscles to promote an erect posture (Tambosco et al., 2014). Secondly, the use of cues, which are external stimuli or generated by the patient; may facilitate movements, improve gait parameters (e.g. speed, stride length, cadence) while walking (Spaulding et al., 2013), and minimise freezing episodes (Keus et al., 2007). Thirdly, the use of cognitive movement strategies (CMS), in which a complex movement is transformed to a number of simple movement elements that are performed in a defined sequence; may improve the performance of complex and simultaneous activities, such as transfers (Keus et al., 2007).

All the above considerations were applied in the current exercise protocol, apart from the CMS; due to time restrictions of each exercise bout and total length of the training period. However, both the educational programme (section 8.9), and the 'individualised home-based exercise booklet' (section 8.10.2) informed the participants about the role of CMS to improve transfers, giving relevant examples. With respect to cues, both visual and auditory cues were selected. The visual cues were looking and following the instructor's movements, and stripes placed on the floor; whereas the auditory cues were the verbal instructions for the performance of exercises.

#### 8.8.2. The exercises of the training protocol

The next step was the selection of specific exercises for the training protocol. The exercises were adopted or modified from effective experimental studies, guidelines and exercise booklets for PD and depression. Furthermore, some exercises were based on the knowledge and previous experience of the chief investigator, who had already designed exercise booklets for PD and for the prevention of falls in senior population. Lastly, the advice of two experienced physiotherapists in PD was asked.

The training protocol was mainly focused on lower limbs once a week, whereas the second weekly session was mainly on upper limbs exercises. The training protocol included only

low-cost, non-sophisticated and portable equipment; such as ankle weights and elastic bands for strengthening exercises. Each exercise bout started with exercise in seated position to ensure participants' safety. Similarly, exercises in upright position started at the third week of training. All the types of exercise were performed during the whole training period, apart from the gait exercises which started at the third week. The full standard protocol can be found in supplement 3, whereas the majority of exercises are presented with images in the 'Individualised home-based exercise booklet (supplement 6-7). Alternative exercises were proposed for patients with difficulties in performing the prescribed exercises, or using a walking aid, for safety and practical reasons. Special emphasis was given to the correct erected position during the exercise performance. Thus, in the first session the patients were taught to sit down or stand up appropriately, and correct their posture during the exercise bout, if needed.

#### *Range of movement (ROM) exercises*

The low intensity ROM exercises aimed to improve or maintain the ROM of joints; and hence, the performance of functional activities (Sakellari et al., 2005). The ROM exercises were performed in the whole available ROM of each movement in a seated position. The speed of movement was moderate (one to two seconds to cover the whole available ROM), and ten repetitions of each movement were performed (O' Brien, 1998). They included exercises for the upper and lower limbs, and the trunk. Emphasis was given to the movements of joints that tend to be reduced in PD; such as trunk rotation and neck extension (van de Kolk and King, 2013). All the exercises are presented in table 8.7 (p. 184).

**Table 8.7.** Brief description of the ROM exercises.

No	Exercise	Exercise position	Progression
01	Chin tucks	Sitting	None
02	Cervical spine (neck) rotation (left-right)		
03	Cervical spine (neck) flexion-extension		
04	Cervical spine (neck) lateral flexion (left-right)		
05	Lumbar and thoracic spine (trunk) rotation (left-right)		
06	Scapula adduction		
07	Shoulder circles (backwards direction)		
08	Shoulder flexion-extension		
09	Elbow flexion-extension		
10	Finger abduction		
11	Hip abduction-adduction		
12	Knee flexion-extension		
13	Ankle dorsiflexion-plantarflexion		

### *Respiratory exercises*

Concerning respiratory exercises, emphasis was given to inspiratory training; because 56.7% of PD patients develop a restrictive obstructive disease, whereas less present an obstructive or mixed pattern (Baille et al., 2016). Inspiratory muscle strength training and deep inspiration breath are recommended to improve pulmonary function (Köseoglu and Tomruk, 2001; Keus et al., 2013), whereas diaphragmatic breathing helps to adopt a normal pattern of breathing (Cianci, 2014). Based on these recommendations, the respiratory training included three exercises, which are presented in table 8.8.

**Table 8.8.** Brief description of the respiratory exercises.

No	Exercise	Exercise position	Progression
01	Diaphragmatic breathing	Sitting	None
02	Breathing-enhanced upper extremity exercises (horizontal abduction of shoulders)		Week 2-4: end-inspiratory hold  Week 5-8: sniff and end-inspiratory hold
03	IMT using a Threshold IMT device		Increase of work load (2 cm H <sub>2</sub> O every week)

Acronyms and abbreviations. H<sub>2</sub>O: water; IMT: inspiratory muscle training.





**Image 8.2.** IMT training using a Threshold IMT device.

The inspiratory muscle training (IMT) was performed using a Threshold IMT device (image 8.2). The analytical description of the respiratory exercises is presented in appendix 8.57.

### *Muscle strengthening exercises*

The muscle strengthening was focused on the weak and elongated muscles, resulted from rigidity, to improve functional ability; and all the muscle groups of the lower limbs, which may be weak due to sedentary lifestyle, to improve balance and prevent from falls (King and Horak, 2009; David et al., 2012). A resistive programme of the lower limbs may also have effects on gait parameters; such as stride length and velocity (Hass et al., 2012). Thus, in the current study, in accordance to the National Parkinson Foundation (NPF) (Cianci, 2014), the muscle strengthening exercises included the following muscle groups of the trunk, and the upper and lower limbs: shoulder flexors, extensors and abductors; scapula elevators and abductors; lumbar extensors; hip extensors, flexors, abductors, and adductors; knee extensors and flexors; and ankle plantarflexors.

A progressive resistance training protocol was designed, because it has been shown to improve muscle strength in mild to moderate PD (Lima et al., 2013); and it is also proposed by the EPDA (Keus et al., 2013). The parameters of strengthening exercises were adopted from disease-specific recommendations and relevant previous studies in PD, and guidelines in the overall population and chronic diseases.

As it was reported in Section 8.8.1, the exercise intensity was moderate; however, there was no special stable equipment to measure 1-RM, and perform the resistive training. Hence, portable equipment was used as resistance against the movement. However, the most effective type of equipment for strength training in patients with PD is not known yet (Tambosco et al., 2014). Thus, elastic bands (Thera-bands) (Keus et al., 2013), free weights (plastic water bottles) (PSC, 2003), and ankle weights (Gallo and Garber, 2011) were selected as external resistance. Lastly, patient's body weight acted as resistance for the closed chain exercises of the lower limbs (Gallo and Garber, 2011). The initial resistance and the progression of exercises was based on previous experimental studies in mild to moderate PD, and relevant recommendations (PSC, 2003; Goodwin et al., 2011; Morris et al., 2011; McGinley et al., 2012). Specifically, the progression of exercises was achieved by: adjusting the number of repetitions; increasing the resistance (Goodwin et al., 2011; Morris et al., 2011; McGinley et al., 2012); and reducing hand support, while performing an exercise behind a chair. The following portable equipment was used to increase the resistance: bottle waters of 0.5, 0.75 and 1 litre, adjustable ankle weights with eight iron weights of 0.25 kilos each, and 1.5 metre length red, green and blue Thera-bands, with a resistance at 100% elongation 1.7, 2.1 and 2.6 kilos respectively (APTA, 2012).

Multi-joint and larger muscle group exercises preceded single-joint and smaller muscle-group exercises (ACSM, 2009; Keus et al., 2013). Thus, the sequence of the exercises for the lower limbs was from the central to peripheral joints. Isotonic (concentric and eccentric) muscle contractions were preferred instead of isometric exercises (ACSM, 2009), as it seems that isometric exercises strengthen the muscles in a particular part of the joint angle (Kleisouras, 1997). One to two sets of eight to 15 repetitions were performed for each muscle group (Keus et al., 2013). The rest period between the sets was one minute, which is the minimum rest recommended by Kleisouras (1997) for moderate intensity (40%-60% RM). Participants were encouraged to move through the full available ROM, and the exercise speed was two seconds for the whole movement (ACSM, 2009). Tables 8.9 (p. 187) and 8.10 (p. 188) provide a brief description of strengthening exercises and their progression levels respectively, whereas a strengthening exercise can be seen in image 8.3 (p. 187).



**Image 8.3.** Hip abduction using elastic bands.

**Table 8.9.** Brief description of the strengthening exercises.

No	Exercise	Exercise position	Exercise resistance
01	Shoulder flexion	Sitting	Bottle of water
02	Shoulder extension (hyperextension)	Sitting	Bottle of water
03	Shoulder abduction	Sitting	Bottle of water
04	Scapula elevation	Sitting	Bottle of water
05	Scapula adduction	Sitting	Elastic band
06	Lumbar extension	Sitting	Body weight and ankle weight on the chest
07	Hip extension	Standing	Ankle weight
08	Hip abduction	Sitting	Elastic band
09A	Knee extension	Sitting	Ankle weight
		*Hold a bottle of water above knees for isometric contraction of hip adductors	
09B	Knee extension	Standing	Body weight
		*Hold a bottle of water above knees for isometric contraction of hip adductors	
10A	Ankle plantarflexion	Sitting	Elastic band
10B	Ankle plantarflexion	Standing	Body weight

**Table 8.10.** Progression levels of strengthening exercises.

No	Exercise	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
01	Shoulder flexion	1 set	1 set	2 sets	2 sets	2 sets	2 sets	2 sets	2 sets
02	Shoulder extension (hyperextension)	10 rep.	12 rep.	10 rep.	12 rep.	8 rep.	10 rep.	8 rep.	10 rep.
03	Shoulder abduction	bottle	bottle	bottle	bottle	bottle	bottle	bottle	bottle
04	Scapula elevation	0.5 L	0.5 L	0.5 L	0.5 L	0.75 L	0.75 L	1 L	1L
05	Scapula adduction	1 set	1 set	2 sets	2 sets	2 sets	2 sets	2 sets	2 sets
		10 rep.	12 rep.	10 rep.	12 rep.	8 rep.	10 rep.	8 rep.	10 rep.
		elastic band red	elastic band red	elastic band red	elastic band red	elastic band green	elastic band green	elastic band blue	elastic band blue
06	Lumbar extension	1 set	1 set	2 sets	2 sets	2 sets	2 sets	2 sets	2 sets
		10 rep.	15 rep.	10 rep.	15 rep.	10 rep.	15 rep.	10 rep.	15 rep.
						ankle weight 1 kg	ankle weight 1 kg	ankle weight 1.5 kg	ankle weight 1.5 kg
						*The ankle weight was hold with both arms in from of the chest			
07	Hip extension			2 sets	2 sets	2 sets	2 sets	2 sets	2 sets
				10 rep.	12 rep.	8 rep.	10 rep.	8 rep.	10 rep.
				ankle weight 0.75 kg	ankle weight 0.75 kg	ankle weight 1 kg	ankle weight 1 kg	ankle weight 1.5 kg	ankle weight 1.5 kg
				*Progressive reduced of hand support					
08	Hip abduction	1 set	1 set	2 sets	2 sets	2 sets	2 sets	2 sets	2 sets
		10 rep.	12 rep.	10 rep.	12 rep.	8 rep.	10 rep.	8 rep.	10 rep.
		elastic band red	elastic band red	elastic band red	elastic band red	elastic band green	elastic band green	elastic band blue	elastic band blue
09A	Knee extension	1 set	1 set						
		10 rep.	12 rep.						
		ankle weight 0.75 kg	ankle weight 0.75 kg						
09B	Knee extension			1 set	1 set	2 sets	2 sets	2 sets	2 sets
				10 rep.	12 rep.	8 rep.	10 rep.	12rep.	15 rep.
				*Progressive reduced of hand support					
10A	Ankle plantarflexion	1 set	1 set						
		10 rep.	12 rep.						
		elastic band red	elastic band red						
10B	Ankle plantarflexion			1 set	1 set	2 sets	2 sets	2 sets	2 sets
				10 rep.	12 rep.	8 rep.	10 rep.	12rep.	15 rep.
				*Progressive reduced of hand support					

Abbreviations. kg: kilograms; L: litre; rep.: repetitions.

*Co-ordination exercises*

The aim of co-ordination exercises was to improve the synchronisation of movements between the two sides of the body. In PD, one side is more affected than the other, and kinetic symptoms (e.g. bradykinesia) are more obvious in one side of the body (Djaldetti et al., 2006). As a result, it is difficult for patients to synchronise movements between the left and right part of their body, and ADLs are hampered (Huang et al., 2012). Co-ordination exercises of the upper and lower limbs were selected in the current training protocol, lasting for one to two minutes each. Similarly to the CMS, before the initiation of the exercise, patients were recommended to plan and mentally visualise the movement. Then, they had to synchronise their movements with the verbal instructions provided by the chief investigator. A brief description of the co-ordination exercises is provided in the table 8.11. As seen in the table, the progression was mainly achieved by increasing movements' speed.

**Table 8.11.** Brief description of the co-ordination exercises.

No	Exercise	Exercise position	Progression	Weeks that the exercise was performed
01	Finger exercises between the thumb and the other fingers separately in both directions	sitting	1. One hand → both hands at the same time  2. ↑ speed  3. holding a straw	1-8
02	Plantarflexion / dorsiflexion alternately	sitting	↑ speed	1-3
03	Hand touch the same side knee three times	sitting	↑ speed	1-3
04	Hand touch the opposite site knee	sitting	↑ speed	4-6
05	Arm swinging in opposite directions	sitting	↑ speed	4
06	Marching on the spot with arm swing	sitting	↑ speed	5-6
07	Marching on the spot without arm swing	standing	↑ speed	5-6
08	Marching on the spot with arm swing	standing	↑ speed	7-8

Symbols. ↑: increase; →: to.

*Balance exercises*

Balance training aimed to improve balance and minimise the number of falls (Cianci, 2014; Keus et al., 2013). Their combination with other training modalities including in the current protocol, such as strength and gait training, may be more effective in reducing the falls number (Van der Kolk and King, 2013). The balance activities of the training protocol and their levels of progression are described in table 8.12. The duration of each exercise was between one and two minutes. During balance training in the seated position, participants were taught not to rest their back on the chair. The progression of exercises was achieved by reducing: the base of support, hand support, and visual input. External forces to maintain balance through anticipatory adjustments were not used, as they seem insufficient in the PD population (Ward and Robertson, 2003). This is probably, because balance impairments in PD are not only caused by extrinsic factors, but mainly by intrinsic factors related to the symptoms of the disease (Sakellari et al., 2005). Lastly, group balance exercises (ball games) were preferred (Kronhed et al., 2001), instead of independent reaching exercises (Morris et al., 2011); as group ball exercises seem more enjoyable, and promote cooperation and socialisation between the trainees (Kronhed et al., 2001).

**Table 8.12.** Brief description of the balance exercises.

No	Exercise	Exercise position	Progression	Weeks that the exercise was performed
01	Shoulder flexion in 90 <sup>0</sup> and opposite hip flexed	Sitting position	Eyes open → eyes closed	1-2
02	One hip flexed	Sitting position	1. Both shoulders abducted in 90 <sup>0</sup> → arms hold opposite shoulder  2. Eyes open → eyes closed	1-2
03	Group ball exercises*	Sitting and standing position	Sitting → standing position	1-8
04	Stepping in all directions (forwards, backwards, side steps)	Standing position	1. Eyes open → eyes closed  2. ↓ hand support	3-6
05	Single limb standing	Standing position	↓ hand support	7-8

\* throwing and catching balls in different directions.

Symbols. ↓: reduce; →: to.

*Gait exercises*

The aim of gait exercises was the improvement of the qualitative characteristics of walking (e.g. stride length, arm swinging, heel first), and re-education of additional accompanying kinetic problems (FOG, body posture) (Sakellari et al., 2005). Cues were applied to increase the patients' attention, and facilitate automatic movement and movement initiation (Keus et al., 2004). However, it is unknown whether all the PD patients benefit from the use of cues, and the characteristics of PD patients that benefit more (Keus et al., 2013). Visual and auditory cues were selected for the gait protocol; because evidence supports their effects on improving gait parameters, FOG episodes and number of falls (Lim et al., 2005; Muñoz-Hellín et al., 2013).

Regarding visual cues, as there is not enough evidence to draw strong conclusions about the preferred type of visual stimuli (Muñoz-Hellín et al., 2013), lines on the ground were used in the present study. These are stable marks, which assist patients to focus on their gait pattern, while participating in a group exercise programme (Ward and Robertson, 2003). The recommendations by Sakellari et al. (2005) were followed for the design of the visual cues. The path length for walking forwards was six metres long, and it was well visually defined. In each exercise room, there were two to three walking paths, allowing at least two participants to exercise in the same time. Transverse lines, 2.5 cm wide, were placed on the floor. The colour of the lines was in contrast with that on the floor. It has been proved that these characteristics have influence on PD population (Sakellari et al., 2005). The transverse lines were placed 50 centimetres apart, as the average stride length in early PD usually varies from 46 to 76 centimetres (Webster, 1968). The minimum normal stride length was selected to allow all the participants to walk with confidence, regardless their somatometric characteristics and the stage of the disease.

With respect to auditory cues, verbal instructions were used instead of a metronome. Although there is a sufficient number of high quality studies to support the use of the metronome to improve gait parameters, such as gait velocity and stride length (Spaulding et al., 2013); it was declined after the pilot work (see Section 8.12). On the contrary, it is

not possible to draw firm conclusions about the effectiveness of verbal instructions in PD population; due to the limited number of relevant studies of low quality, which have assessed the effectiveness of verbal instructions after the end of a single exercise bout (Fok et al., 2011). However, due to metronome's rejection; verbal instructions were applied on gait activities around a chair, backwards and forwards walking. The verbal instructions were kept simple ('take big steps', 'swing arms when walking', 'heel first') in order to not confuse the patients.

With regard to the forward walking, the verbal instructions were added the sixth week. The combination of visual and auditory cues may lead to dual task activities (Sakellari et al., 2005), which should be avoided in the early stages of training (Keus et al., 2013), because they may be associated with higher risk of falls and FOG episodes (Keus et al., 2004). On the contrary, more recent published research indicates that walking under dual task conditions in PD may lead to larger steps and gait velocity (Brauer and Morris, 2010).

In addition, attentional and proprioceptive strategies were selected to facilitate the movement and improve the qualitative characteristics of gait pattern. In attentional strategies, the participants had to think about the whole performance of movement (e.g. upright position of the head, erected body posture, arm swing, heel first, big steps) in advance (Keus et al., 2013). Special emphasis was given to the upright position of the head, as much as possible. Patients were asked to look straight at a fixed body while walking. The upright positioning of the head may activate the proprioceptors in the neck, contributing to the normal body posture (Sakellari et al., 2005). Proprioceptive strategies were used at the initiation of walking, as they may assist freezers to overcome FOG episodes and initiate the movement. Proprioceptive strategies included: rocking from left to right, marching on the spot and one step backwards (King and Horak, 2009; Brauer et al., 2011). In addition, during forwards walking, participants were asked: to walk across the path, to turn in 'clock' (on the spot) pattern, to avoid FOG, and to continue back (Almeida and Bhatt, 2012).



The gait training included six activities (table 8.13), two of them in freezing-provoking situations. The participants were focused on qualitative aspects of walking performance (Sakellari et al., 2005). At the end of training, the physiotherapists were giving feedback to patients, to try to improve all the gait aspects in the following session (Keus et al., 2013). Participants using a walking stick, were instructed to perform these exercises with their equipment, which acts as an horizontal visual cue at foot level (Rubinstein et al., 2002). The total duration of gait training was between six and ten minutes.

**Table 8.13.** Brief description of gait exercises.

No	Exercise	Description	Progression	Weeks that the exercise was performed
01	Walking forwards in the walking path	Visual cues on the floor	Add verbal instructions ('arm swing', 'heel first')	3-8
02	Walking backwards	Verbal instructions ('big steps')	None	5-6
03	Walking on a coloured line sideways	Visual cues on the floor	Add verbal instructions ('big steps')	7-8
04	Walking around a chair in 'arc' pattern	Walking forwards. Verbal instructions ('big steps')	None	3-4
05	Sudden starts and stops while walking forwards*	Walking in the walking path. Verbal instructions for stop and start ('stop'. 'start')	None	5-6
06	Moving in eight figures around two chairs*	Walking forwards. Verbal instructions ('big steps')	Reduce distance between chairs (1.50m, 1.20m.)	7-8

\* activities in freezing-provoking situations

### *Stretching exercises*

The general aim of stretching exercises was the restoration of the entire ROM and the characteristic flexed posture, usually adopted by PD patients (Sakellari et al., 2005). However, it is unclear whether the increase in ROM is caused by the increased length of the muscles, or by the increased tolerance of subjects to stretching (Knudson, 2006). In the current study, the stretching exercises focused on the shortened muscles, due to rigidity,

as proposed by the NPF (table 8.14) (Cianci, 2014). Static active and passive (using assistance provided by the gravity and body's weight) self-stretches were preferred. Static stretches are performed easily; they are safe, as there is no high risk for injury; and are recommended in mild to moderate PD (Gallo and Garber, 2011; Page, 2012b). In addition, self-stretches allow participants to control the end-feel of the stretch (Page, 2012b). The movement speed from the initial to the final position was relatively slow; as it seems that a slow velocity does not activate the myotatic reflex, caused by the rapid muscle length, and the rapid muscle contraction is avoided (Kleisouras, 1997). In the general population, evidence indicates that the greatest change in ROM with a static stretch occurs when the final position is held between 15 and 30 seconds (Page, 2012b). This duration is similar to the recommendations in PD population, ranging from 10 to 30 seconds (Gallo and Garber 2011; Cianci 2014). As Gallo and Garber (2011) recommend 60 seconds of total stretching time for each stretching exercise, in the current study, it was decided to perform two stretches of 30 seconds each. Patients were advised to feel the stretch like a gentle pull, do not stretch to the point of pain to prevent injuries, and remain motionless while holding the stretch (Cianci, 2014).

**Table 8.14.** Brief description of the stretching exercises.

No	Muscle stretching	Position	Description	Weeks that the exercise was performed
01	Pectorals and flexor muscles of the trunk	Seated	Extension of the trunk, horizontal abduction of both arms, extension of cervical spine	1-8
02A	Biceps brachii	Seated	Extension of both elbows and shoulders	1-2
02B	Biceps brachii	Upright	On the wall. Extension of elbow and shoulder	3-8
03	Wrist flexors	Seated	Wrist extension of both hands	1-8
04	Hamstrings	Seated	Knee extension and flexion of the trunk, if possible	1-8
05A	Calves	Seated	Knee extension and ankle dorsiflexion with the use of an elastic band	1-2
05B	Calves	Upright	On the wall. Knee extension and ankle dorsiflexion	3-8

*Aerobic exercise (walking)*

Aerobic exercise is a suggested component of training programmes in PD and the clinically depressed population to improve cardiorespiratory fitness and emotional well-being (CPG 2008; Keus et al., 2013). Although there is more evidence to support the effectiveness of treadmill training to improve gait parameters and cardiorespiratory fitness in PD population (Keus et al., 2013; van de Kolk and King, 2013); the exercise venues were not equipped with treadmills, stationary bicycles or elliptical trainers. Walking is an alternative form of physical activity that has the potential to improve aerobic capacity and alleviate depression (Robetson et al., 2012); and it is recommended by international organisations in healthy adults and chronic diseases (Cianci 2004; Nelson et al., 2007), in PD (PSC, 2003; Keus et al., 2013), and depression (CPG, 2008). Walking has the advantages of being an enjoyable and free mode of exercise, with minimal risk of adverse effects; and easily undertaken by most people (Stokes, 2004). When taken outdoors, an attractive natural environment may decrease levels of stress (Robetson et al., 2012). Hence, individualised, outdoors or indoors, non-supervised walking was selected as the mode of aerobic training in the current study.

The participants were instructed to walk outdoors or indoors (e.g. mall) at least 150 minutes per week (Nelson et al., 2007; Cianci, 2014). The recommended frequency and duration was 30 minutes a day, five times a week. The exercise intensity was moderate (40-60% HR<sub>max</sub>); and patients were advised to walk at a comfortable self-selected pace, with a preferred intensity between five and six on a ten-point Borg scale (Nelson et al., 2007; Keus et al., 2013). The patients could rest for a few minutes or reduce their walking speed in case of fatigue. It was also recommended, for safety reasons, to be accompanied by another person. Participants with low levels of physical activity, could split the daily walking time into smaller segments; and gradually increase the duration of the walking bout, and walking speed (Cianci, 2014; Craft and Perna, 2004).

### **8.9. Design of the group educational programme**

The aim of the group educational programme was to improve the patients' knowledge about PD and ways to overcome the daily difficulties arising from the symptoms of the disease. The educational programme was designed by the author of the present thesis in co-operation with the lecturers, who delivered the sessions. The whole design was based on relevant recommendations in PD (Keus et al., 2004), and previous experimental studies in PD (Guo et al., 2009).

The programme composed of eight sessions lasting approximately 30 minutes, which were scheduled once a week, after the end of the exercise bout. The lectures included background information about PD, pharmacological and non-pharmacological management (e.g. surgical operation, dietician and psychological advice, physiotherapy-therapeutic exercise), advice on ADLs, and education about falls. The titles of the lectures and their content are presented in table 8.15 (p. 197). The education sessions were delivered by relevant experienced professionals for prestige reasons, to provide accurate information, and able to response to the participants' questions. The educational programme was delivered with the use of PowerPoint presentations, through a PowerPoint projector. The recommendations by Finkelstein and Samsonov (2008) were followed for the design of PowerPoint presentations to facilitate the lecture and attract learners. The PowerPoint presentations are presented in supplements 8-9. The language of lectures was as simple as possible, in order the patients to understand simple medical terms, especially relevant to the pathophysiology and symptomatology of the disease. Some lectures were designed as an interactive dialogue, rather than a traditional lecture. Patients were also encouraged to share their own experiences and beliefs. Thus, the lectures, promoted the communication, and socialisation between the participants (Brox et al., 2008; Guo et al., 2009).

**Table 8.15.** The lectures of the group educational programme.

No	Title of lecture	Content of lecture	Lecturer's occupation
01	Understanding PD (I)	<ul style="list-style-type: none"> <li>• Pathophysiology of PD</li> <li>• Symptoms of PD</li> </ul>	Neurologist
02	Understanding PD (II)	<ul style="list-style-type: none"> <li>• PD diagnosis</li> <li>• PD pharmacological management</li> <li>• Surgical operation in PD</li> </ul>	
03	Diet in PD	<ul style="list-style-type: none"> <li>• Importance of diet in PD</li> <li>• The role of dietitians in PD</li> <li>• General advice about diet in PD</li> </ul>	Dietician
04	Psychology in PD	<ul style="list-style-type: none"> <li>• The psychology of PD patients</li> <li>• The role of psychologists in PD</li> <li>• General advice about psychological disturbances in PD</li> </ul>	Psychologist
05	Physiotherapy in PD'	<ul style="list-style-type: none"> <li>• Aims of physiotherapy in PD</li> <li>• Types of exercises in PD</li> </ul>	Physiotherapist*
06	Transfers in PD'	<ul style="list-style-type: none"> <li>• Advice to improve transfers</li> <li>• Walking aids in PD</li> </ul>	
07	Advice in ADLs	<ul style="list-style-type: none"> <li>• Advice to improve the performance of ADLs</li> </ul>	
08	Keep active	<ul style="list-style-type: none"> <li>• Additional healthcare professionals for the management of PD</li> <li>• Alternative exercises in PD</li> <li>• Falls in PD</li> </ul>	

\*chief investigator

### 8.10 Design of the study's booklets

Two booklets were designed for the present study by the author, and delivered to participants, entitled: 'Group exercise booklet', 'Individualised home-based exercise booklet'.

#### 8.10.1. Group exercise booklet

The 'Group exercise booklet' (supplements 4-5) provided the subjects of the IG information about: the exercise venue, the timetable of the exercise and educational sessions, their duties during the intervention period, indications for termination of exercise, walking and falls. A two-month walking diary was included in the 'Walking' part, and a two-month FD and FQs in the 'Falls' part. The participants were requested to complete the FD and the FQ, if a fall occurred. Furthermore, they had to fill out the walking diary indicating the days and

the duration they walked. The walking diary was used as a feedback to check their walking activity, and their weekly progress. As the IG consisted of six groups, six versions of the booklet were printed.

#### 8.10.2. Individualised home-based exercise booklet

The aim of the 'Individualised home-based exercise booklet' (supplements 6-7) was to provide the patients with a variety of exercises and adequate instructions to perform the training programme on their own at home. The rationale for the selection of exercises did not differ from those reported in the group exercise programme (section 8.8). The home-based exercises were grouped in six categories. However, in contrast to the group-based exercise programme; the booklet did not include gait exercises at home for safety reasons, as the training was unsupervised. Instead of it, there was advice for indoor walking. Before the presentation of exercises, advice about the appropriate erect posture was provided. The proposed exercises were performed either in seated or upright position, except from one (code: B4), which was done in lying position.

Apart from the proposed exercises, the booklet contained: background information about PD, using short questions and answers; advice about training at home, and transfers; and a 'Walking' and 'Falls' part, as described in the 'Group exercise booklet' (section 8.10.1), including a walking diary, a FD, and FQs. The instructions for the exercises, transfers and indoor walking were accompanied by appropriate images to facilitate the performance of movements. A healthy male adult was preferred as a model for the pictures of the booklet, as he was able to perform all the movements in an appropriate way. Before the photo shooting, the aim of the study and the booklet was explained to him. He had 24 hours to decide his participation or not; and signed on a consent form (Appendices 8.58-8.59). His facial characteristics were covered to protect his anonymity.

Regarding the training programme; subjects were instructed to exercise four times a week, for 30 to 45 minutes in each session. If this was not possible, shorter sessions could be

combined, to make up a total of 30-45 minutes exercise each day (Sakellari et al., 2005). They were taught one day to exercise their upper limbs, and the following the lower limbs; following the instructions that were provided through the booklet. In each session, participants had to select exercises from all the exercise categories, and complete the exercise diary. The diary was used to document the type and duration of exercise performed. At the end of the intervention and follow-up period, the diary was checked by the research team to ensure that the participants were exercised regularly. Lastly, similar to the group exercise, participants were instructed to walk at least 2.5 hours on a weekly basis (section 8.8.2), and complete the walking diary, FD and FQ (section 8.10.1). Two versions of the booklet were printed: one for the members of the CG including a five-month walking diary; and one for the IC with a three-month walking diary.

### **8.11. Ethical consideration**

The ethical principles of the RCT did not differ significantly from those of survey (Section 5.6). The current subchapter provides additional information relevant to the current RCT. All procedures followed during the study were in accordance with the Hellenic National Standards of Physiotherapeutic Ethics (PPTA, 2007) and the ethical principles for medical research, as presented by the World Medical Association in the Helsinki Declaration (WMA, 2008).

Apart from the ethical approval for the entire study (section 5.6.1); an additional approval was granted by the HPDA (Appendix 8.60) on 2<sup>nd</sup> February 2015 to conduct the current step; in order to protect the rights, safety, dignity and well-being of those who participated in the study. The nature and the purpose of the study were explained to participants before the initiation of the study; and the study's information sheet (appendices 8.4-8.5), which was given to them, provided an overview for the whole study. They had the right to withdraw at any time of the study, access their personal information, and get informed about the results of the study. A consent form was signed by all the participants, before the start of the intervention (Appendices 8.6-8.7); and by the model used for the photo shoot (Appendices 8.58-8.59).

Anonymity of the participants (Section 5.6.4), as well as confidentiality (Section 5.6.3) of their personal information were ensured; whereas it was prohibited to the participants and the research team, to report to third people the names of patients that participated in the study. Only two volunteers (psychologist and secretary) and the president of the HPDA had access to the database of participants with their contact details and other personal information. Even the researcher was unaware about the contact details of participants and had no access to this database. The RCT guaranteed justice, and exploitation was avoided. In particular, all the participants were treated fairly and equally through the whole study, as standardised intervention and assessment protocols were followed. No member of the research team accepted financial reward or other gifts from the participants, and was not paid by them for medical and allied health care.

The study possessed no risk for participants and the topic of the research was not sensitive. The whole study design was suitable for the target population and minimised the harm risk. Both the assistant physiotherapists and the participants, before the start of the intervention, were informed about safety considerations indications for stopping exercise, adopted by the American College of Sports Medicine (ACSM, 2014) (Appendix 8.61). All the healthcare professionals had the knowledge and experience to provide acute care in case of an emergency. In case of health issues during the study period, the participants were taught to inform the research team. The programme allowed a maximum number of absences, that it could be used for health issues to prevent participants for any harm. They were also advised to stop any exercise and rest for a while, if they were unable to perform it, due to fatigue. Lastly, as none of the participants was paid to take part in the study, they did not feel obligated to take part, even if they were not certain.

### **8.12. Pilot study**

An initial study was conducted two months before commencing classes. Its length was three weeks, lasting from 19<sup>th</sup> January 2015 to 6<sup>th</sup> February 2015.



### 8.12.1. Aim of the pilot study

The purpose of conducting a pilot study is to examine the feasibility of an approach that is intended to be used in a larger scale study (Leon et al., 2011). The specific objectives of the current pilot work were:

- To ensure whether the screening and assessment tools were suitable for the study population.
- To test the feasibility of exercises and their parameters (e.g. sets and repetitions) included in the group exercise programme and the individualized home-based exercise programme.
- To test whether the instructions and pictures of the booklet were adequate and understandable.
- To ensure whether the most disabled would be able to complete the programme.
- To estimate the completion time of the assessments and exercise sessions.
- To receive feedback for the final design of all the components of the proposed RCT.

### 8.12.2. Design of the pilot study

Only the exercises of both study groups were piloted, and not the entire intervention, due to restricted time. Thus, the pilot study was a modified small-scale version of the research study. Specifically:

- It was a non-RCT.
- The intervention period lasted only two weeks. Hence, the group training was not progressive, as designated for the main study; however all the exercises were tested.
- Clinical depression, as detected by the HADS-D, was not an inclusion criterion.
- The SQ was not included in the assessments.
- The educational sessions, follow-up assessment and result analysis were not performed.

Hence, the IG participated in a two-week group exercise programme; whereas the CG in a two-week individualised home-based exercise programme. The pilot work (IG training and

assessments) carried out at the offices of 'Parkinson Care', as there was an empty room suitable for the group exercise programme and the assessments. The research team included three healthcare professionals: the chief investigator, an assistant physiotherapist and a neurologist. All of them were also involved in the main study.

### 8.12.3. Participants

The subjects were recruited from the patients list of the neurologist, who participated in the study. Six patients with PD participated in the pilot work; four in the IG, and two in the CG. All of them were under stable antiparkinsonian medication. With respect to the IG, it was decided to select at least one individual from each PD stage, using the H&Y scale, in order to see how patients with different levels of PD severity react to the training programme. The major demographic characteristics and the health status of participants are presented in table 8.16 (p. 203). Only three participants were identified with clinical depression using the HADS-D subscale; and only one was clinically diagnosed with depression, before the onset of PD.

The patients were informed about the aim of the study and signed the relevant consent form (Appendix 8.6 and 8.7). None of them participated in the main study, due to possible training effects. However, they were able to participate in the group exercise programmes at the end of the study, offered to the members of the CG. When the intervention was completed, a semi-structured interview was performed by the chief investigator; and the participants expressed their opinion about the group training and the study's booklets. The basic questions of the interview are presented in Appendix 8.62.

**Table 8.16.** Demographic characteristics and health status of participants.

Code	Group	Gender	Age (in years)	H&Y stage	Years since PD diagnosis	Freezing	Independent walking	HADS-D at baseline	Clinical diagnosis of depression
01	IG	M	60	1	1	NF	Y	8	N
02	IG	F	58	2	3	NF	Y	5	N
03	IG	M	71	3	9	NF	Y	10	Y
04	IG	M	68	3	7	FR	Y	11	N
05	CG	M	62	1.5	1	NF	Y	4	N
06	CG	F	70	3	8	NF	Y	2	N

Acronyms and abbreviations. CG: comparison group; F: female; FR: freezer; H&Y: Hoehn and Yahr; IG: intervention group; M: male; N: no; NF: non-freezer; Y: yes.

#### 8.12.4. Modifications in the study protocol

Feedback of participants was generally positive about study's design. However, regarding the measurement tools, it was decided to select the 2MWT instead of 6MWT to assess the exercise tolerance. The 6MWT exhausted the patients, especially on three H&Y stage. In addition, its long duration, in combination with the other measurement tools exceeded an hour.

With respect to the group exercise programme, the followed modifications were made, based on participants' comments and chief investigator's judgment:

- The use of metronome as an auditory cue in gait exercises was rejected, because it was not considered practical for the current study. As the walking exercises took place simultaneously for all the participants; there was inability of participants to synchronise their steps with metronome's sound; probably due to different disability level. Thus, verbal instructions were preferred.
- Due to limited time of each exercise bout and total length of the intervention, it was decided to exclude facial exercises, and functional exercises (e.g. writing), from the training protocol; as other types of exercise were considered more relevant with the

aims and objectives of the study. Furthermore, the duration of some exercises was reduced. For instance, two sets of muscle strengthening exercises were preferred instead of three.

- The CMS exercise from sitting to standing was declined, because it was impossible for patients with different disease severity to synchronise their movements with the researcher's instructions. Hence, it was decided to inform the patients of the IG about the role of the CMS through the educational programme (Section 8.9).
- Strengthening and stretching exercises to improve the sideways tilting of the trunk were not included in the main study; because not all the PD patients had Pisa's syndrome, and some individuals may have the tendency to lead on the left side, whereas others on the right.
- Alternative strengthening exercises were designed, in case that some participants were unable to perform some exercises in upright position, or whether the overhead movements were reduced due to another condition (e.g. adhesive capsulitis).

Lastly, the following modifications in the 'Individualised home-based exercise booklet' were made:

- Some exercise instructions were re-written in a simpler way in order to be understandable by the patients.
- Strengthening exercises with elastic bands and ankle weights were not included in the final version, as they would not be provided to the patients.
- The 'near fall' definition was deleted from the booklet, because it was difficult for some patients to distinguish the difference between the 'fall' and 'near fall' definition.

### **8.13. Main study**

The current section describes thoroughly the implementation of the main study. However, a briefly description of the research design was already reported in the section 8.2.5. Following the completion of the pilot study and the modifications in study's design (section 8.12), and as the number of potential participants was satisfactory, the main study was conducted from March 2015 to March 2016. The study's flowchart is presented in figure 8.2 (p. 207). The intervention started after the random allocation of participants to the

study groups (Section 8.5.7). During the main study, all the subjects were allowed to continue their routine activity, and receive their usual care; which apart from the pharmacological treatment, it could be non-pharmacological treatment (e.g. speech therapy, occupational therapy, dietary advice). However, they did not undergo any other form of physiotherapy-therapeutic exercise and psychotherapy (e.g. CBT), to ensure the results were due to the current intervention.

The members of the IG participated in an eight-week ( $\approx 2$  months) 'group exercise and educational programme' (sections 8.8 and 8.9). They were also walking independently on a weekly basis; and they were required to complete by themselves the walking diary, the FD and the FQs, which were found in the 'Group-exercise booklet' (section 8.10.1). Their duties were reminded on a weekly basis, during the exercise classes. One training and educational group was made in each municipality, apart from Argypoli-Elliniko, where two groups were running, based on the number of participants. The exercise and educational classes were held from Monday to Saturday, apart from public holidays. The start and end date of the group programmes in each municipality is reported in table 8.17 (p. 206).

During the three-month ( $\approx 13$  weeks) follow-up period, the members of the IG independently continued their exercises at home and walking activity, using the instructions of the 'Individualised home-based exercise booklet' (section 8.10.2). This booklet was given to them at the last session of the intervention programme, and instructions were provided about how to use it. The patients were contacted via telephone, once a week, by the chief investigator or the volunteers (secretary, psychologist), to ensure: their participation in the fitness programme; the completion of the walking diary, FD and FQs; and if their medication remained stable. Telephone calls may also increase the adherence of participants to an unsupervised exercise programme, and minimise the drop-out rate (Ravenek and Schneider, 2009). The telephone number of the HPDA was used for this purpose. The participants had to bring the 'Group exercise booklet' and the 'Individualised home-based exercise booklet' at the post-intervention and follow-up

assessment respectively. The research team checked whether the individualised programme was followed on a regular basis, and received the completed FD and FQs.

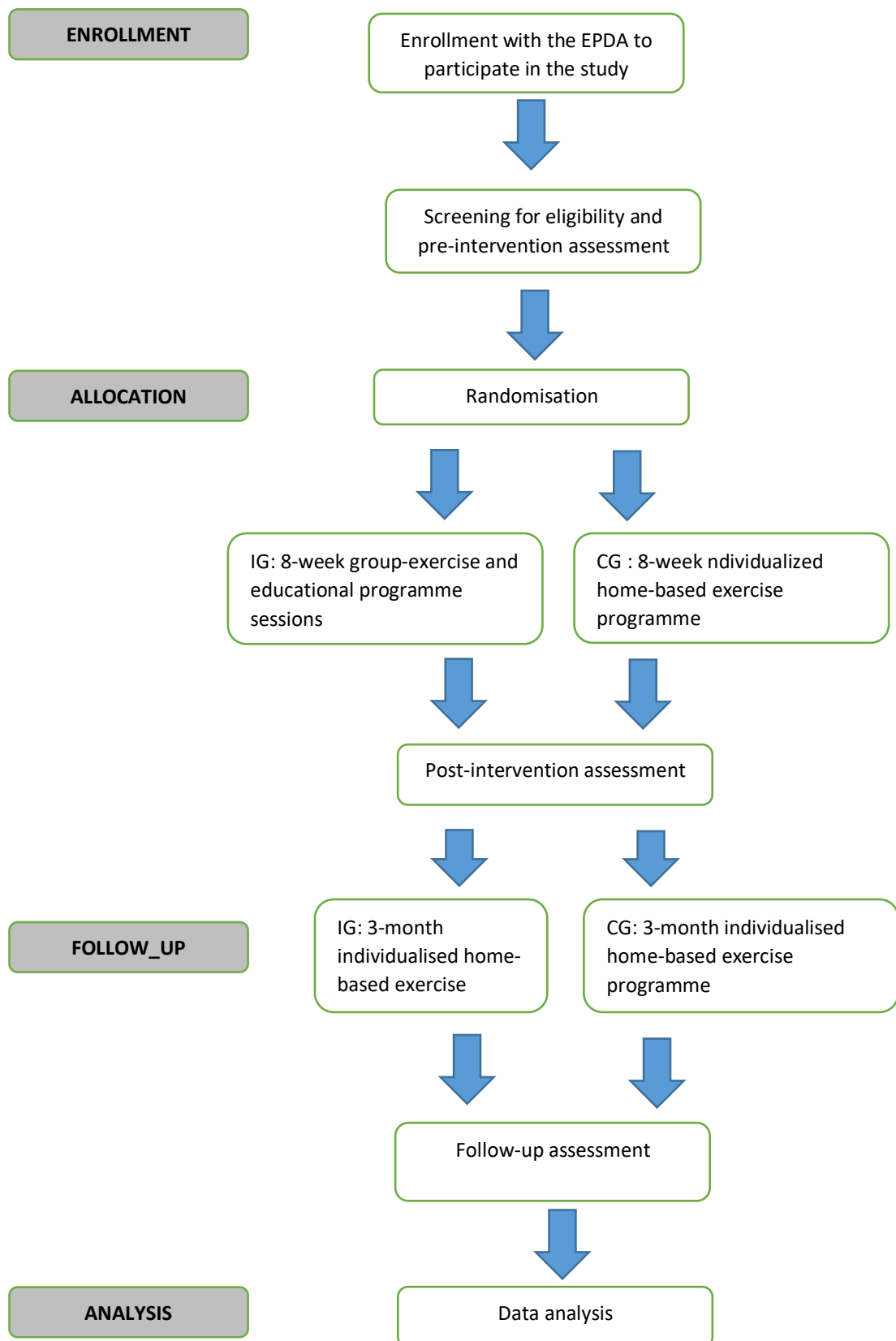
The members of the CG participated in a five-month individualised home-based exercise programme, based on the booklet 'Individualised home-based exercise booklet' (section 8.10.2). Similarly to the IG, the research team contacted them once a week, and they were asked to bring the booklet at the post-intervention and follow-up assessments.

The subjects in the IG and CG had to complete the 'group exercise and educational programme' and the 'unsupervised individualised home-base exercise programme' at least 85% accuracy. This ensured that all the participants of the IG and CG received the same intervention (Hackney and Earhart, 2010). Patients with more absences were excluded from the study. Lastly, it should be stated that the follow-up period in both study groups, commenced after the end of post-intervention assessment in each municipality.

**Table 8.17.** Start and end date of the intervention in each municipality.

Municipality	Start date	End date
Argyroupoli-Elliniko *	16 <sup>th</sup> April 2015	11 <sup>th</sup> June 2015
Galatsi	7 <sup>th</sup> October 2015	2 <sup>nd</sup> December 2015
Ilioupoli	21 <sup>st</sup> April 2015	16 <sup>th</sup> June 2015
Paleo Faliro	16 <sup>th</sup> May 2015	11 <sup>th</sup> July 2015
Peristeri	1 <sup>st</sup> April 2015	27 <sup>th</sup> May 2015

\* two intervention groups



Acronyms. CG: comparison group; IG: intervention group.

**Figure 8.2.** Study's flowchart.

#### 8.14. Data analysis

Before the data analysis, the coding of participants was performed. The participants' codes were a combination of capital letters and numbers. The letters indicated the municipality in which each patient participated, either in the IG or the CG. Thus, the letters 'AE' were selected for the municipality of Argyroupoli-Elliniko, 'GA' for Galatsi, 'IL' for Ilioupoli, 'PE' for Peristeri, and for 'PF' for Paleo Faliro.

Quantitative and qualitative techniques were selected for the analysis and interpretation of data, based on the research aim and objectives of the present study. All the data, apart from the FQ and SQ, were converted into numerical values and quantitative analysis was used. The qualitative analysis followed for the FQ and SQ is described in Section 5.9.2. Similarly to survey's qualitative analysis, two investigators (the PhD student and a physiotherapist with previous experience in qualitative analysis) were involved to increase validity, and a translator was consulted for the conceptual translation of some phrases from the Greek to English language.

With respect to the quantitative analysis, the following outcome measures were examined: depression (as measured by the HADS-D), anxiety (as measured by the HADS-A), psychological distress (as measured by the HADS), QoL (as measured by the PDQ-39 and its domains), functional balance (as measured by the BBS), FOF (as measured by the FES-I), functional mobility (as measured by the TUG test), exercise tolerance (as measured by the 2MWT), and lung function (as measured by spirometry: FVC %, FEV1 %, FEV1/FVC %, IVC %).

Quantitative data were analysed using SPSS (version 22.0). After having defined (named and coded) all the variables, descriptive and inferential statistics were selected. Descriptive statistics were applied to analyse the socio-demographic features and health status. Percentages, means (SD) and median were used for this purpose. Inferential analysis was



used to explore differences between different study's groups or measures, or explore relationships between variables. Significance was set at  $p < .05$  (Pallant, 2016).

Normal distribution was assessed by the Shapiro Wilks test (Hicks, 2009). The Shapiro-Wilks test was preferred instead of Kolmogorov-Smirnov, because it is the most powerful test to assess normality for all sample sizes, especially when the population is less than 2,000 (Ghasemi and Zahediasl, 2012). Of those variables with normal distribution ( $p > .05$ ), parametric tests were applied. When data were not normally distributed or categorical, alternative non-parametric tests were selected (Pallant, 2016).

Three between-group comparisons were performed, to assess differences between the IG and CG at: baseline, post-intervention and follow-up. Of those variables with normal distribution; comparison between means was performed by independent sample t-tests. For the data not normally distributed, the alternative non-parametric Mann-Whitney U test was used. When a statistical significant difference was found, the direction of the difference was explored by comparing the median values. Lastly, Chi-square tests for independence were applied among two categorical variables to explore differences between two groups at baseline (Pallant, 2016).

The within-group comparison for the IG and CG was performed by one-way repeated measures of One-way Analysis of Variance (ANOVA), when data were normally distributed, because there was one group of subjects measured in three different times (baseline, post-intervention, follow-up). Where the results of ANOVA indicated significance between groups (Group effect), post hoc analysis (Bonferroni) was carried out, to find the groups that differed significantly. The alternative non-parametric, Friedman test was selected, when data were not normally distributed; and the Wilcoxon Signed Rank Test, as post-hoc testing, if a statistically significant difference was found somewhere among the three time points (Pallant, 2016).

With respect to the between- and within-group comparison, the importance of findings was calculated using the effect size. The eta squared or partial eta squared was calculated for parametric tests. In particular, after performing independent samples t-test the eta squared was calculated using the formula:  $\text{Eta squared} = \frac{t^2}{t^2 + (N_1 + N_2 - 2)}$ ; where  $N_1$  and  $N_2$ , the number of subjects per group. The effect size for the one-way repeated ANOVA was given by the partial eta squared (Pallant, 2016). These values were interpreted as: small ( $= .01$ ), moderate ( $= .06$ ), or large ( $= .14$ ) effect (Cohen, 1988). The effect size for the non-parametric tests (Mann-Whitney U test and Wilcoxon Signed Rank Test) was calculated by the formula:  $r = z / \sqrt{N}$ ; where  $N$ , the total number of cases (Pallant, 2016). These values were interpreted as: small ( $r = .10-.29$ ), medium ( $r = .30-.49$ ), or large ( $r = .50-1.00$ ) effect (Cohen, 1988). Apart from the significant difference and the effect size, the study aimed to identify clinical differences between the groups and clinical changes within the groups, making comparisons between the MCID value for each measurement tool and the difference in means for each outcome measure.

Bivariate correlational techniques were also used for the assessment of the relationship (strength and direction) among anxiety and depressive levels and the participants' anthropometric characteristics (e.g. age), and features related to PD (e.g. years since PD diagnosis); as well as other outcome measures (e.g. FES-I). All these variables were continuous or dichotomous. In particular, the relationship between normally distributed variables was assessed by Pearson Correlation co-efficient ( $r$ ); whereas the Spearman correlation co-efficient ( $r_s$ ) among the variables, which did not present a normal distribution. A co-efficient up to .09 indicated a very small strength of relationship, between .10 and .29 a small, from .30 up to .49 a medium, and between .50 and 1.00 a large relationship (Pallant, 2016).

Lastly, a logistic regression was used to predict the factors (independent variables) that contributed significantly to falls (dependent variables) (Pallant, 2016). Anthropometric data (e.g. age) and features related to PD (e.g. years since PD diagnosis) were used as independent variables.

### 8.15. Summary of Chapter 8

- An RCT was designed to investigate the short and longer-term effects of an eight-week, multimodal, progressive, supervised, community-based group exercise and education class, in people affected with PD and comorbid depression; comparing them to a CG following an unsupervised, individualised home-based exercise programme.
- Depression, as measured by the HADS-D, was the primary aim of the study.
- The author designed the group-based exercise and educational programme, and the two study's booklets. The whole design was based on the combined recommendations of organisations and results of previous effective studies in PD and depressed population.
- Before the implementation of the main study, a pilot work was conducted to examine the feasibility of the approach.
- The main study was held in five municipalities of Athens Metropolitan Area, Greece, between March 2015 and March 2016.
- The subjects were recruited from the HPDA, and the municipalities where the study was undertaken, through: internet, printed announcements and media.
- Based on the sample size determination, 70 patients were participated in the study.
- During the two-month intervention period, the IG participated in a combined community group-based exercise and educational programme; whereas the CG in an individualised home based exercise programme, based on the instructions of a booklet. During the three-month follow-up period, both groups followed the individualised home-based training.
- With respect to the IG, the group-exercise programme was performed indoors, twice a week. The programme was progressive, and the duration of each exercise bout was 60 minutes. It included the following types of exercises: ROM, respiratory, muscle strengthening, co-ordination, balance, gait, stretching and walking. Individualised walking was performed outdoors, five times a week. The educational programme consisted of eight thirty-minute lectures to inform patients about PD and assist them to overcome the daily difficulties arising from the symptoms and signs of the disease.
- The individualised, home-based, unsupervised exercise programme; was held four times a week. The duration of each exercise bout was 30-45 minutes. It included: ROM,

respiratory, strengthening, co-ordination, balance and stretching exercises; plus walking outdoors five times a week.

- The study assessed: psychological and functional (mobility) status, number and circumstances of falls, QoL, respiratory function, and patients' satisfaction about the group exercise programme.
- Appropriate tools with high clinimetric properties, translated and validated in the Greek language, were selected for the screening procedure and the assessments. Four additional instruments (GHQ, FD, FQ, SQ) were designed by the chief investigator.
- The HADS was selected both as a screening tool to detect depression and anxiety, and an assessment tool to measure the response to the treatment.
- Both qualitative and quantitative approaches were applied for the data analysis. The effects of the intervention were explored by: statistical and clinical significance, effect size, and the subjective view of participants, based on their answers in the SQ.

# **CHAPTER 9**

## **RCT – RESULTS**

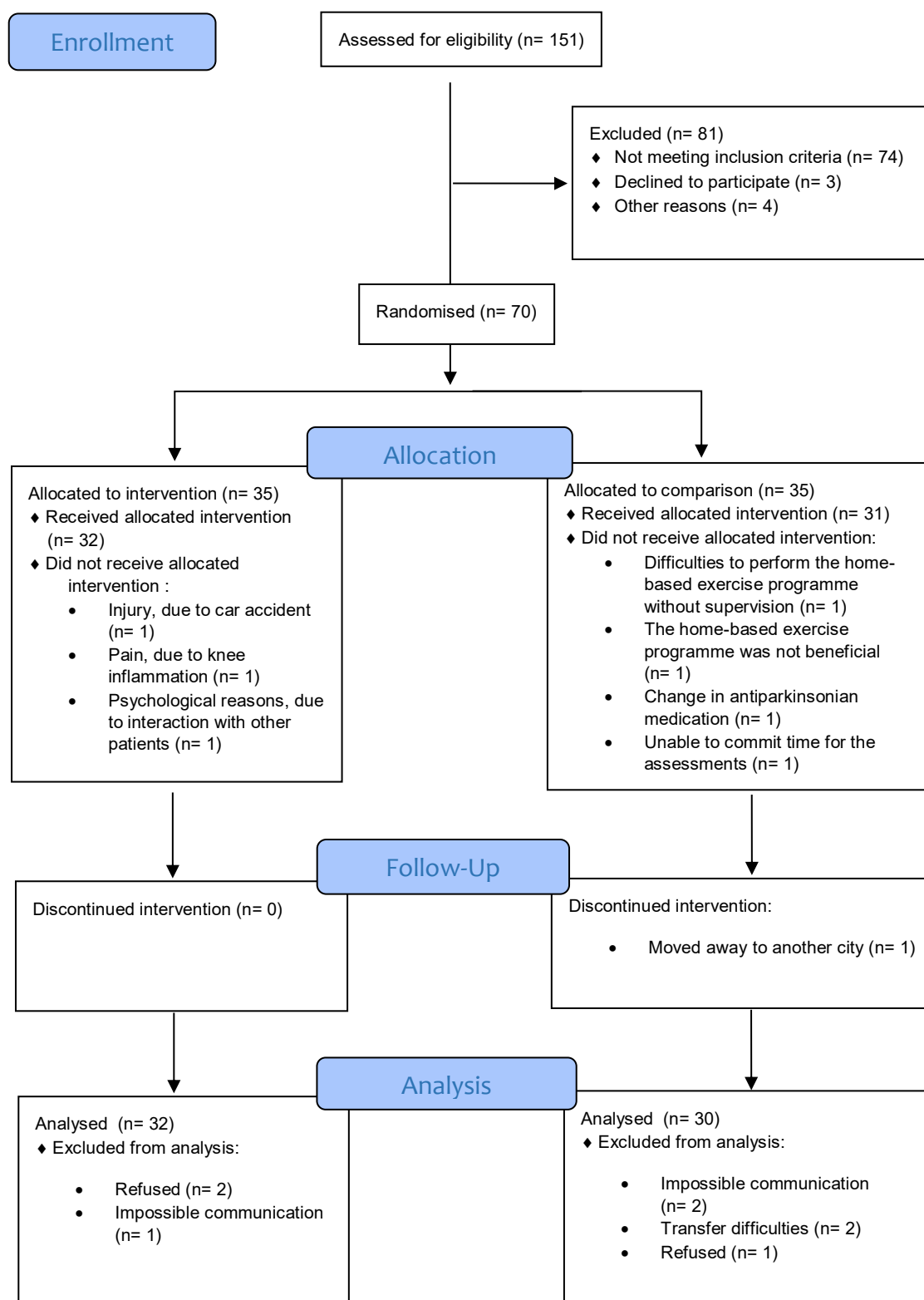
### 9.1. Introduction

The current chapter includes the presentation of the results of the RCT, using quantitative and qualitative approaches. In the tables, continuous variables are presented as mean ( $\pm$ SD), when data were normally distributed; and median in non-normally distributed data. With respect to the effect size, the eta or partial eta squared is written for parametric data; and the value of  $r$ , for non-parametric data. In addition, the categorical variables are presented as absolute (number of individuals or falls) and relative frequencies (percentages).

### 9.2. Number of participants, drop-out reasons and attendance rate

Following screening, 70 patients with PD were eligible to take part in the study. Both groups comprised of 35 individuals. During the intervention period seven individuals, three from the IG and four from the CG, discontinued the study. During the follow-up period, one more subject from the CG abandoned the study. Thus, the drop-out rate for the whole sample, for the entire period of study (from the baseline to follow-up), was 13.3%. However, the drop-out rate was lower in the IG (8.6%), compared to the CG (14.2%). Finally, 62 individuals -32 from the IG and 30 from the CG- completed the study and included in the analysis. Figure 9.1 (p. 215) presents the patients' journey through the whole study period.

As seen in figure 9.1 (p. 215), the main drop-out reasons in both groups were not related to the training programme itself. However, one participant of the IG at H&Y stage one stated that: *"I want to quit the programme...the interaction with other patients doesn't help me. Before the start of the class, they discuss about their daily difficulties and the side effects of medication...Here, I see people with more serious problems than me...This provokes stress to me. I'm thinking of my future...and I'm afraid of it."* (IL07). Regarding the CG, one participant discontinued the programme, because he found the exercises of the booklet quite difficult to perform them without supervision; whereas a woman at the third week of the intervention stated: *"I decided to stop the exercise at home. I have not seen any improvement yet."* (AE16).



**Figure 9.1.** Patients' journey through the whole study period

Attendance rates were calculated based on the total initial number of participants in each study group ( $n = 35$ ). With respect to the IG, the overall attendance at the exercise classes was 83% (465 out of a possible 560 sessions), and at education classes 77% (216 out of 280 sessions). The attendance rate for the CG, during the two-month intervention period, was not calculated, because it was based on subjective data given by the patients to the research team through the weekly telephone contacts.

Lastly, there were no missing data for any outcome measure. In cases of an absence at the assessments or when the chief investigator deemed it clinically unsafe to perform the clinical tests; an additional appointment was arranged as soon as possible. Concerning the self-report questionnaires; only the full-completed HADS, PDQ-39 and FES-I were included in the analysis in order to not violate the total scores and scores of subsections. Similarly to the survey, the FQ was considered completed and included in the analysis, if at least the half items had been answered (Iarossi, 2006).

### **9.3. Socio-demographic characteristics and health status**

#### **9.3.1. Socio-demographic characteristics and features related to Parkinson's disease**

Table 9.1 (pp. 217-218) indicates that there were no significant differences between the two groups in all the socio-demographic characteristics and features related to PD at baseline, apart from UPDRS-I subscale (mentation, behavior, and mood) ( $p = .01$ ,  $z = -2.37$ ), where the CG had worse scores [ $5.57 (\pm 2.3)$ ]. All the participants were Caucasians, aged between 48 and 89 years old, and males (54.8%) were more than females (45.2%). Regarding BMI, 33 patients were classified as overweight (BMI: 25.0-29.9 kg/m<sup>2</sup>), 12 as obese type I (BMI: 30.0-34.9 kg/m<sup>2</sup>), and six as obese type II (BMI: at least 35 kg/m<sup>2</sup>). The majority of patients (46.8%) attended at least one year of secondary education (high school or technical school), and 17 were graduates or attended at least one year of tertiary education (University, College or higher technical school). An interesting finding was that despite the fact that the retirement age in Greece was 65 years (67 since 2015), 90.3% of participants were not working.



Concerning PD, its duration since diagnosis ranged between five months and 12 years. The total UPDRS score and the UPDRS-III (motor evaluation) score ranged from 16 to 57 and from 5 to 26, respectively. In addition, 37.1% of participants were categorised as fallers, reporting at least one fall the last two months prior the start of the intervention. Lastly, ten patients were using a walking stick, either a simple ( $n=8$ ) or tripod walking stick ( $n=2$ ), and none used a walking frame.

**Table 9.1.** Socio-demographic characteristics and features related to Parkinson's disease at baseline for the whole sample, IG and CG.

Variable		All (n= 62)	Intervention Group (n= 32)	Comparison Group (n= 30)	P value
Municipality of enrollment	Argyroupoli- Elliniko	17 (27.4%)	9 (28.1%)	8 (26.7%)	$p = .99$ $\chi^2 = .24$
	Ilioupoli	11 (17.7%)	5 (15.6%)	6 (20%)	
	Paleo Faliro	11 (17.7%)	6 (18.8%)	5 (16.7%)	
	Peristeri	12 (19.4%)	6 (18.8%)	6 (20%)	
	Galatsi	11 (17.7%)	6 (18.8%)	5 (16.7%)	
Gender	Male	34 (54.8%)	17 (53.1%)	17 (56.7%)	$p = .98$ $\chi^2 = .77$
	Female	28 (45.2%)	15 (46.9%)	13 (43.3%)	
Nationality	Greek	59 (95.2%)	30 (93.8%)	29 (96.7%)	$p = .59$ $\chi^2 = .31$
	Albanian	1 (1.6%)	1 (3.1%)	0 (0%)	
	Ukrainian	1 (1.6%)	1 (3.1%)	0 (0%)	
	Armenian	1 (1.6%)	0 (0%)	1 (3.3%)	
Marital status	Married	42 (67.7%)	22 (68.8%)	20 (66.7%)	$p = 1.00$ $\chi^2 = .02$
	Separated	8 (12.9%)	4 (12.5%)	4 (13.3%)	
	Windowed	8 (12.9%)	4 (12.5%)	4 (13.3%)	
	Single	2 (3.2%)	1 (3.1%)	1 (3.3%)	
	In a relationship	2 (3.2%)	1 (3.1%)	1 (3.3%)	
Educational level	Primary	16 (25.8%)	8 (26%)	8 (26.7%)	$p = .98$ $\chi^2 = .14$
	Secondary	29 (46.8%)	15 (46.9%)	14 (46.7%)	
	Tertiary	17 (27.4%)	9 (28.1%)	8 (26.7%)	
Employment status	Retired	46 (74.2%)	25 (78.1%)	21 (70%)	$p = .18$ $\chi^2 = .33$
	Household	10 (16.1%)	6 (18.8%)	4 (13.5%)	
	Employee	6 (9.7%)	1 (3.1%)	5 (16.7%)	
H&Y stage	1	9 (14.5%)	5 (15.6%)	4 (13.3%)	$p = .96$ $\chi^2 = .38$
	1.5	5 (8.1%)	2 (6.2%)	3 (10%)	
	2	12 (19.4%)	7 (21.9%)	5 (16.7%)	
	2.5	10 (16.1%)	5 (15.6%)	5 (16.7%)	
	3	26 (41.9%)	13 (40.6%)	13 (43.3%)	
Walking	Independent	52 (83.9%)	25 (78.1%)	27 (90%)	$p = .35$ $\chi^2 = .85$
	Walking aid (stick)	10 (16.1%)	7 (21.9%)	3 (10%)	
Freezing	Freezers	13 (21%)	7 (21.9%)	6 (20%)	$p = 1.00$ $\chi^2 = .02$
	Non freezers	49 (79%)	25 (78.1%)	24 (80%)	
Falls	Fallers	23 (37.1%)	12 (37.5%)	11 (36.7%)	$p = 1.00$ $\chi^2 = .00$
	Non fallers	39 (62.9%)	20 (62.5%)	19 (63.3%)	
SEADL	50%	2 (3.2%)	2 (6.2%)	0 (0%)	$p = .66$ $\chi^2 = .22$
	60%	10 (16.1%)	5 (15.6%)	5 (16.7%)	
	70%	18 (29%)	8 (25%)	10 (33.3%)	
	80%	19 (30.6%)	10 (31.2%)	9 (30%)	
	90%	12 (19.4%)	6 (18.8%)	6 (20%)	
	100%	1 (1.6%)	1 (3.1%)	0 (0%)	

Variable	All (n= 62)	Intervention Group (n= 32)	Comparison Group (n= 30)	P value
Age in years	70.69 ( $\pm$ 8.52)	70.87 ( $\pm$ 7 .62)	70.52 ( $\pm$ 9.49)	p = .87 t = .16
Height (in centimetres)	166.69 ( $\pm$ 7.96)	167.67 ( $\pm$ 8.00)	165.69 ( $\pm$ 7.92)	p = .95 t = .34
Weight (in kilos)	77.89 ( $\pm$ 12.98)	79.05 ( $\pm$ 13.14)	76.69 ( $\pm$ 12.93)	p = .48 t = .69
BMI (kg/m <sup>2</sup> )	28.11 ( $\pm$ 4.48)	28.28 ( $\pm$ 5.03)	27.94 ( $\pm$ 3.91)	p = .78 t = .28
MMSE total score	28 *	28 *	28 *	p = .73 z = -.33
Years since PD diagnosis	5 *	4.5 *	5.98 ( $\pm$ 3.2)	p = .87 z = -.15
UPDRS total score	41 *	39.63 ( $\pm$ 10.87)	40.00 ( $\pm$ 11.46)	p = .90 t = -.12
UPDRS-I score (mentation, behaviour and mood)	4.64 ( $\pm$ 2.48)	3 *	5.57 ( $\pm$ 2.3)	p = .01 z = - 2.37
UPDRS-II score (activities of daily living)	13 *	13.73 ( $\pm$ 4.41)	13.55 ( $\pm$ 4.93)	p = .88 t = .14
UPDRS-III score (motor examination)	19 *	19*	17.48 ( $\pm$ 4.83)	p = .36 z = - .89
UPDRS-IV score (complications of therapy)	4 *	4 *	4 *	p = .84 z = -.20

\* median (for non-parametric data)

Acronyms. BMI: Body Mass Index; H&Y stage: Hoehn and Yahr stage; MMSE: Mini Mental State Examination; n: number of participants; PD: Parkinson's disease; SEADL: Schwab-England Activities of Daily Living; UPDRS: Unified Parkinson's disease Rating Scale.

### 9.3.2. Co-morbidities

The mean number of co-morbid conditions per participant was 2.3. Only six individuals (9.7%) were free of co-morbidities, whereas 49 (79%) reported at least two comorbidities. The number of participants who reported at least one co-morbidity from each category is presented in table 9.2 (p. 219), whereas the analytical list of comorbidities and previous surgical operations in Appendix 9.1. Chi squares tests for independence revealed no significant differences between the IG and CG ( $p > .05$ ).

**Table 9.2.** Types of co-morbidities in the study population.

Type of co-morbidities	All (n= 62)	Intervention Group (n= 32)	Comparison Group (n= 30)	P value
Cardiovascular disease	24 (40.6%)	12 (40%)	12 (41.3%)	p = 1.00 $\chi^2 = -.02$
Respiratory disease	2 (3.3%)	1 (3.3%)	1 (3.4%)	p = 1.00 $\chi^2 = -.00$
Musculoskeletal disease	41 (69.4%)	19 (63.3%)	22 (75.8%)	p = .37 $\chi^2 = -.14$
Neurological disease*	2 (3.3%)	1 (3.3%)	1 (3.4%)	p = 1.00 $\chi^2 = -.00$
Other disease **	29 (49.1%)	15 (50%)	14 (48.2%)	p = .79 $\chi^2 = .61$

\*neurological disease apart from PD

\*\*diseases or conditions that could not be included to the previous categories (i.e. hyperlipidemia, thyroid disease)

Abbreviations. n: number of participants.

### 9.3.3. Parkinson's disease medication

All participants were receiving antiparkinsonian medication (table 9.3, p. 220). The medication was classified into six categories, according to the NICE Guidelines (NICE, 2006). Twelve patients were treated with one-drug therapy (19.3%), whereas a two and a three-drug therapy were administrated to 50 patients (80.7%). An interesting finding was that only four patients were not treated with L-dopa, as in these cases a DA agonist was combined with a MAO-B inhibitor, a recommended two-drug therapy in PD (Rao et al., 2006). In addition, no participants were treated with catechol-O-methyltransferase (COMT) inhibitors. However, the drug Stalevo, which was administrated to 19 patients, apart from L-dopa, contains two additional active substances: carbidopa and entacapone. Entacapone is a COMT inhibitor.

**Table 9.3.** Administrated antiparkinsonian medication to participants.

Types of PD medication	All (n= 62)	Intervention Group (n= 32)	Comparison Group (n= 30)	P value
L-dopa	58 (93.5%)	30 (93.7%)	28 (93.3%)	p = 1.00 $\chi^2 = .94$
DA Agonists	27 (45.7%)	15 (50%)	12 (41.4%)	p = .96 $\chi^2 = .76$
MAO-B inhibitors	19 (32.2%)	10 (33.3%)	9 (31%)	p = .45 $\chi^2 = .28$
Amentadine	5 (8.4%)	3 (10%)	2 (6.8%)	p = .50 $\chi^2 = .17$
Anticholinergics	2 (3.3%)	1 (3.3%)	1 (3.4%)	p = .97 $\chi^2 = .29$
COMT inhibitors	0 (0%)	0 (0%)	0 (0%)	

Abbreviations. COMT: Catechol-O-methyltransferase; DA: dopamine; L-dopa: levodopa; MAO-B: monoamine oxidase-B; n: number of participants; PD: Parkinson's disease.

#### 9.3.4. Depression

Although, the HADS-D subscale identified all the participants as depressed (HADS-D score at least eight) during the screening procedure; only 37.1% of them had been officially diagnosed with depression, by a medical doctor or psychologist, either before or after PD diagnosis (table 9.4).

**Table 9.4.** Number of participants with or without official clinical diagnosis of depression.

Official diagnosis of depression		All (n= 62)	Intervention Group (n= 32)	Comparison Group (n= 30)	P value
No		39 (62.9%)	19 (59.4%)	20 (66.7%)	p = .74 $\chi^2 = -.07$
Yes	Before PD diagnosis	9 (14.5%)	3 (9.4%)	6 (20%)	
	After PD diagnosis	14 (22.6%)	10 (31.2%)	4 (13.3%)	

Abbreviations. n: number of participants; PD: Parkinson's disease.

A further analysis revealed that antidepressant drug therapy was administered to 25 out of 62 (40.3%) participants. Nineteen of them had been officially diagnosed with depression, whereas six not. Despite the fact that four individuals had been diagnosed in the past with

depression, they did not receive any relevant pharmacological treatment during the study period. On the contrary, although six participants had never been officially diagnosed with depression, they were under antidepressant therapy. Table 9.5 provides information relevant to the antidepressant medication the participants received, which was grouped into five categories (Kupfer, 2005). 17 patients were treated with one drug therapy, whereas eight with two-drug therapy.

**Table 9.5.** Types of antidepressant medication and number of receivers.

Types of antidepressant medication	All (n= 62)	Intervention Group (n= 32)	Comparison Group (n= 30)
SSRIs	15	9	6
SNRIs	8	3	5
TCAs	2	1	1
MAOIs	1	0	1
Atypical antidepressants	7	4	3

Abbreviations. MAOIs: Monoamine oxidase inhibitors; n: number of participants; SNRIs: Serotonin-norepinephrine reuptake inhibitors; SSRIs: Selective serotonin reuptake inhibitors; TCAs: Tricyclic antidepressants.

An additional interesting fact is that five patients were treated with anxiolytic drugs (Benzodiazepine or Benzodiazepine derivatives), and four with antipsychotic drugs (Atypical antipsychotic). The majority of them (seven out of nine) were also under antidepressant medication. Lastly, four out of five patients that were under anxiolytic medication, scored at least eight in the HADS-A subscale at baseline.

## 9.4. Outcome measures: Between-group comparisons

### 9.4.1. Between-group comparison at baseline

With respect to the outcome measures, the between-group comparison did not reveal any significant difference ( $p > .05$ ) between the IG and CG at baseline (table 9.6, p. 222). As seen, the effect sizes were small for all the variables.

**Table 9.6.** Between-group comparison at baseline.

Outcome measure		Intervention group Mean (SD)	Comparison group Mean (SD)	P value	Effect size
HADS	Anxiety	8.88 (± 4.61)	8.23 (± 3.09)	p = .52 t = .62	.00
	Depression	10 *	10 *	p = .30 z = -1.01	.12
	Total	19 *	18 *	p = .98 z = -.21	.00
PDQ-39	Mobility (%)	44.31 (± 21.51)	35.87 (± 19.28)	p = .11 t = 1.58	.03
	ADL (%)	37*	35*	p = .13 z = -1.48	.03
	Emotional well-being (%)	49.81 (± 20.27)	44.87 (± 17.82)	p = .31 t = 1.01	.01
	Stigma (%)	31 *	22*	p = .28 z = -1.06	.13
	Social support (%)	10 *	12 *	p = .99 z = -.00	.00
	Cognition (%)	35.18 (± 20.01)	31.33 (± 18.83)	p = .41 t = .81	.01
	Communication (%)	25 *	25 *	p = .98 z = -.02	.00
	Bodily discomfort (%)	36.72 (± 17.55)	33.90 (± 13.63)	p = .48 t = .70	.00
	Summary Index (%)	32*	32*	p = .44 z = -.76	.09
FES-I		37.80 (± 9.44)	35.00 (± 10.91)	p = .29 t = 1.05	.01
BBS		46 *	46 *	p = .76 z = -.30	.00
TUG (seconds)		13 *	11.5 *	p = .92 z = -.99	.01
2MWT	Walking distance (metres)	85.02 (± 24.77)	82.53 (± 27.72)	p = .71 t = .36	.00
Spirometry	FVC (%)	88*	89*	p = .97 z = -.03	.00
	FEV <sub>1</sub> (%)	90.57 (± 20.49)	94.45 (± 21.75)	p = .48 t = -.70	.00
	FEV <sub>1</sub> / FVC (%)	94 *	96 *	p = .72 z = -.34	.06
	IVC (%)	81.33 (± 17.46)	82.55 (± 16.48)	p = .78 t = -.27	.00

\* median (for non-parametric data)

Acronyms. 2MWT: two-minute walk test; ADL: activities of daily living; BBS: Berg Balance Scale; FES-I: Fall Efficacy Scale-International; FEV<sub>1</sub>: forced expiratory volume in the first second; FVC: forced vital capacity; HADS: Hospital and Anxiety Depression Scale; IVC: inspiratory vital capacity; PDQ-39: Parkinson's disease Questionnaire-39; SD: standard deviation; TUG: Timed Up and Go.

### 9.4.2. Between-group comparison at post-intervention

There were no significant differences ( $p > .05$ ) between the study groups for the primary (depression) and secondary outcomes at the end of the treatment; apart from the HADS total score ( $p = .03$ ,  $t = -2.17$ ), where the effect size indicated a moderate effect ( $\eta^2 = .07$ ) (table 9.7). For the rest outcomes the effect size was small.

**Table 9.7.** Between-group comparison at post-intervention.

Outcome measure		Intervention group Mean (SD)	Control group Mean (SD)	P value	Effect size
HADS	Anxiety	6.81 ( $\pm 3.42$ )	8.03 ( $\pm 2.79$ )	$p = .13$ $t = -1.53$	.03
	Depression	9 *	9.5 *	$p = .07$ $z = -1.75$	.22
	Total	16.03 ( $\pm 4.71$ )	18.70 ( $\pm 4.97$ )	$p = .03$ $t = -2.17$	.07
PDQ-39	Mobility (%)	35.47 ( $\pm 20.43$ )	35.30 ( $\pm 19.02$ )	$p = .97$ $t = .03$	.00
	ADL (%)	27 *	29 *	$p = .52$ $z = -.64$	.08
	Emotional well-being (%)	33 *	41 *	$p = .08$ $z = -1.73$	.21
	Stigma (%)	15 *	25 *	$p = .12$ $z = -1.55$	.19
	Social support (%)	16 *	16 *	$p = .38$ $z = -.87$	.06
	Cognition (%)	31.22 ( $\pm 17.56$ )	30.23 ( $\pm 15.46$ )	$p = .66$ $t = .43$	.00
	Communication (%)	16 *	29 *	$p = .52$ $z = -.62$	.07
	Bodily discomfort (%)	50 *	41 *	$p = .44$ $z = -.72$	.07
	Summary index (%)	30.38 ( $\pm 11.01$ )	32.47 ( $\pm 10.33$ )	$p = .44$ $t = -.77$	.00
FES-I		35.57 ( $\pm 9.27$ )	34.90 ( $\pm 10.93$ )	$p = .80$ $t = .25$	.00
BBS		48.72 ( $\pm 4.53$ )	46.53 ( $\pm 6.38$ )	$p = .12$ $t = 1.56$	.03
TUG (seconds)		10.5 *	11 *	$p = .25$ $z = -1.13$	.15
2MWT	Walking distance (metres)	92.42 ( $\pm 27.24$ )	81.91 ( $\pm 30.37$ )	$p = .16$ $t = 1.40$	.04
Spirometry	FVC (%)	97.20 ( $\pm 25.94$ )	95.00 ( $\pm 19.78$ )	$p = .71$ $t = .36$	.00
	FEV <sub>1</sub> (%)	95.23 ( $\pm 23.36$ )	96.28 ( $\pm 22.37$ )	$p = .86$ $t = -1.75$	.00
	FEV <sub>1</sub> / FVC (%)	97 *	97.5 *	$p = .63$ $z = -0.47$	.05
	IVC (%)	83.40 ( $\pm 17.50$ )	80.93 ( $\pm 15.29$ )	$p = .56$ $t = .57$	.00

\* median (for non-parametric data)

Acronyms. 2MWT: two-minute walk test; ADL: activities of daily living; BBS: Berg Balance Scale; FES-I: Fall Efficacy Scale-International; FEV<sub>1</sub>: forced expiratory volume in the first second; FVC: forced vital capacity; HADS: Hospital and Anxiety Depression Scale; IVC: inspiratory vital capacity; PDQ-39: Parkinson's disease Questionnaire-39; SD: standard deviation; TUG: Timed Up and Go.

### 9.4.3. Between-group comparison at follow-up

The between-group comparison at follow-up did not reveal any significant difference ( $p > .05$ ) in any of the outcome measures between the IG and CG (table 9.8), whereas the effect size was small for all the variables.

**Table 9.8.** Between-group comparison at follow-up.

Outcome measure		Intervention group Mean (SD)	Control group Mean (SD)	P value	Effect size
HADS	Anxiety	7.47 ( $\pm$ 3.53)	8.13 ( $\pm$ 2.63)	$p = .40$ $t = -.83$	.01
	Depression	9 *	10 *	$p = .12$ $z = -1.55$	.19
	Total	16 *	18. *	$p = .23$ $z = -1.18$	.14
PDQ-39	Mobility (%)	38.66 ( $\pm$ 18.90)	33.83 ( $\pm$ 18.17)	$p = .31$ $t = 1.02$	.00
	ADL (%)	37.16 ( $\pm$ 22.76)	34.37 ( $\pm$ 15.11)	$p = .57$ $t = .56$	.00
	Emotional well-being (%)	39 *	41 *	$p = .50$ $z = -.67$	.08
	Stigma (%)	18 *	25 *	$p = .15$ $z = -1.43$	.18
	Social support (%)	16 *	16 *	$p = .67$ $z = -.41$	.05
	Cognition (%)	31.53 ( $\pm$ 16.67)	25.50 ( $\pm$ 14.29)	$p = .13$ $t = 1.52$	.03
	Communication (%)	25 *	25 *	$p = .80$ $z = -.25$	.03
	Bodily discomfort (%)	46.78 ( $\pm$ 19.97)	45.20 ( $\pm$ 12.78)	$p = .54$ $t = .64$	.00
	Summary index (%)	32.31 ( $\pm$ 10.77)	31.50 ( $\pm$ 9.75)	$p = .75$ $t = .31$	.00
FES-I		35.33 ( $\pm$ 8.35)	34.38 ( $\pm$ 10.44)	$p = .69$ $t = .38$	.00
BBS		48 *	49 *	$p = .83$ $z = -.20$	.07
TUG (seconds)		10.5 *	11 *	$p = .47$ $z = -.71$	.10
2MWT	Walking distance (metres)	90.20 ( $\pm$ 27.33)	85.98 ( $\pm$ 28.48)	$p = .56$ $t = .58$	.01
Spirometry	FVC (%)	92*	92 *	$p = .91$ $z = -.10$	.13
	FEV <sub>1</sub> (%)	94.90 ( $\pm$ 22.45)	96.86 ( $\pm$ 20.78)	$p = .72$ $t = -.34$	.00
	FEV <sub>1</sub> / FVC (%)	98.17 ( $\pm$ 11.32)	100.14 ( $\pm$ 10.25)	$p = .48$ $t = -.70$	.01
	IVC (%)	80.5*	81.5 *	$p = .71$ $z = -.36$	.04

\* median (for non-parametric data)

Acronyms. 2MWT: two-minute walk test; ADL: activities of daily living; BBS: Berg Balance Scale; FES-I: Fall Efficacy Scale-International; FEV<sub>1</sub>: forced expiratory volume in the first second; FVC: forced vital capacity; HADS: Hospital and Anxiety Depression Scale; IVC: inspiratory vital capacity; PDQ-39: Parkinson's disease Questionnaire-39; SD: standard deviation; TUG: Timed Up and Go.



## 9.5. Outcome measures: Within-group comparison

### 9.5.1. Within-group comparison: intervention group

Table 9.9 (p. 226) summarises the within group comparison for the IG between the three assessments of the study. In summary, the group-based exercise and educational programme led to many statistically significant improvements, which persisted up to the end of the follow-up period, with medium or large effect sizes. In particular, the Friedman test and the post-hoc Wilcoxon Signed Rank tests revealed that depression (HADS-D) –the primary outcome measure- was statistically significant improved from baseline up to the end of the treatment ( $p = .00$ ), and from baseline to follow-up ( $p = .00$ ). The magnitude of the differences in the means was medium in both cases ( $t1-t2: r = .40$ ;  $t1-t3: r = .31$ ). Regarding the secondary outcomes, statistically significant improvements ( $p \leq .05$ ) emerged up to the follow-up period for: anxiety (HADS-A), with a large effect size (partial eta squared = .31); psychological distress (HADS), with a large effect size (partial eta squared = .34); functional balance (BBS), with a large effect size ( $t1-t2: r = .61$ ;  $t1-t3: r = .59$ ); functional mobility (TUG test); with a large effect size ( $t1-t2: r = .58$ ;  $t1-t3: r = .59$ ); exercise tolerance (2MWT), with a large effect size (partial eta squared: .45); forced vital capacity (FVC), with a medium effect size ( $t1-t2: r = .32$ ;  $t1-t3: r = .34$ ); forced expiratory volume in one second ( $FEV_1$ ), with a large effect size (partial eta squared: .26); and inspiratory vital capacity (IVC), with a medium effect size ( $t1-t3: r = .33$ ). QoL (PDQ-39 SI) was statistically significant improved up to the end of the treatment, whereas its strength of association was medium ( $t1-t2: r = .33$ ). With respect to the subscales of PDQ-39, significant differences up to the follow-up were identified only in three subscales (mobility, emotional well-being, and stigma), whereas the scores of bodily discomfort subscale were worsened.

**Table 9.9.** Within-group comparison for the IG.

Outcome measure		T1 Mean (SD)	T2 Mean (SD)	T3 Mean (SD)	P value	Notes	Effect size
HADS	Anxiety	8.88 ( $\pm$ 4.61)	6.81 ( $\pm$ 3.42)	7.47 ( $\pm$ 3.53)	F = 13.97 p = .00	t1-t2: p= .00 t1-t3: p= .01 t2-t3: p= .00	.31
	Depression	10 *	9 *	9 *	$\chi^2$ = 12.06 p = .00	t1-t2: p= .00 t1-t3: p= .01	t1-t2: r = .40 t1-t3: r = .31 t2-t3: r = .35
	Total	19.34 ( $\pm$ 5.93)	16.03 ( $\pm$ 4.71)	17.12 ( $\pm$ 4.81)	F = 16.52 p = .00	t1-t2: p= .00 t1-t3: p= .00 t2-t3: p= .00	.34
PDQ-39	Mobility (%)	44.31 ( $\pm$ 21.51)	35.47 ( $\pm$ 20.43)	38.66 ( $\pm$ 18.90)	F = 9.83 p = .00	t1-t2: p= .00 t1-t3: p= .00	.24
	ADL (%)	37 *	27 *	35 *	$\chi^2$ = 9.47 p = .00	t1-t2: p= .00	t1-t2: r = .37 t1-t3: r = .19 t2-t3: r = .21
	Emotional well-being (%)	49.81 ( $\pm$ 20.27)	45.73 ( $\pm$ 16.19)	44.37 ( $\pm$ 16.16)	F = 16.55 p = .00	t1-t2: p= .00 t1-t3: p= .00	.34
	Stigma (%)	31 *	15 *	18 *	$\chi^2$ = 16.06 p = .00	t1-t2: p= .00 t1-t3: p= .01	t1-t2: r = .40 t1-t3: r = .40 t2-t3: r = .18
	Social support (%)	10 *	16 *	16 *	$\chi^2$ = 4.29 p = .11		t1-t2: r = .19 t1-t3: r = .13 t2-t3: r = .21
	Cognition (%)	35.18 ( $\pm$ 20.01)	31.22 ( $\pm$ 17.56)	31.53 ( $\pm$ 16.67)	F = 2.04 p = .15		.06
	Com. (%)	25 *	16 *	25 *	$\chi^2$ = .19 p = .90		t1-t2: r = .06 t1-t3: r = .00 t2-t3: r = .03
	Bodily discomfort (%)	36.72 ( $\pm$ 17.55)	44.70 ( $\pm$ 15.28)	46.78 ( $\pm$ 19.97)	F = 13.34 p = .00	t1-t2: p= .00 t1-t3: p= .00	.30
	Summary index (%)	32 *	31.5 *	32 *	$\chi^2$ = 12.20 p = .00	t1-t2: p= .00	t1-t2: r = .33 t1-t3: r = .25 t2-t3: r = .25
FES-I		37.80 ( $\pm$ 9.44)	35.57 ( $\pm$ 9.27)	35.33 ( $\pm$ 8.35)	F = 3.09 p = .08		.09
BBS		46 *	48.5 *	48 *	$\chi^2$ = 42.27 p = .00	t1-t2: p= .00 t1-t3: p= .00	t1-t2: r = .61 t1-t3: r = .59 t1-t3: r = .34
TUG (seconds)		13 *	10.5 *	10.5 *	$\chi^2$ = 42.92 p = .00	t1-t2: p= .00 t1-t3: p= .00	t1-t2: r = .58 t1-t3: r = .59 t2-t3: r = .33
2MWT	Walking distance (metres)	85.02 ( $\pm$ 24.77)	92.42 ( $\pm$ 27.24)	90.20 ( $\pm$ 27.33)	F = 25.64 p = .00	t1-t2: p= .00 t1-t3: p= .00	.45
Spirometry	FVC (%)	88 *	87.5 *	92 *	$\chi^2$ = 13.02 p = .00	t1-t2: p= .01 t1-t3: p= .00	t1-t2: r = .32 t1-t3: r = .34 t2-t3: r = .18
	FEV <sub>1</sub> (%)	90.57 ( $\pm$ 20.49)	95.23 ( $\pm$ 23.36)	94.90 ( $\pm$ 22.45)	F = 11.17 p = .00	t1-t2: p= .00 t1-t3: p= .00	.26
	FEV <sub>1</sub> / FVC (%)	94 *	97 *	98 *	$\chi^2$ = 1.08 p = .58		t1-t2: r = .13 t1-t3: r = .14 t2-t3: r = .08
	IVC (%)	80 *	79.5 *	80.5 *	$\chi^2$ = 7.64 p = .02	t1-t3: p= .00	t1-t2: r = .23 t1-t3: r = .33 t2-t3: r = .07

\* median (for non-parametric data)

Abbreviations. 2MWT: two-minute walk test; ADL: activities of daily living; BBS: Berg Balance Scale; Com.: communication; FES-I: Fall Efficacy Scale-International; FEV<sub>1</sub>: forced expiratory volume in the first second; FVC: forced vital capacity; HADS: Hospital and Anxiety Depression Scale; IVC: inspiratory vital capacity; PDQ-39: Parkinson's disease Questionnaire-39; SD: standard deviation; T1: pre-intervention; T2: post-intervention; T3: follow-up; TUG: Timed Up and Go.

### 9.5.2. Within-group comparison: comparison group

With respect to the CG, no statistically significant differences ( $p > .05$ ) occurred between the three assessments for depression and the majority of secondary outcome measures (table 9.10, p. 228). However, the individualised home-based programme improved significantly ( $p \leq .05$ ) balance (BBS) and functional mobility (TUG test) from baseline to follow-up; whereas the strength of association was large ( $r = .50-1.00$ ). The IVC was significantly improved from post-intervention to follow-up ( $p = .00$ ), and the magnitude of the differences in the means was medium (partial eta squared = .12)

**Table 9.10.** Within-group comparison for the CG.

Outcome measure		T1 Mean (SD)	T2 Mean (SD)	T3 Mean (SD)	P value	Notes	Effect size
HADS	Anxiety	8.23 ( $\pm$ 3.09)	8.03 ( $\pm$ 2.79)	8.13 ( $\pm$ 2.62)	F = .02 p = .79		.00
	Depression	10 *	9.5 *	10 *	$\chi^2$ = 2.18 p = .33		t1-t2: r = .12 t1-t3: r = .17 t2-t3: r = .03
	Total	18 *	17 *	18 *	$\chi^2$ = 2.11 p = .34		t1-t2: r = .15 t1-t3: r = .17 t2-t3: r = .03
PDQ-39	Mobility (%)	35.87 ( $\pm$ 19.28)	35.30 ( $\pm$ 19.02)	33.83 ( $\pm$ 18.17)	F = 1.98 p = .15		.06
	ADL (%)	39.50 ( $\pm$ 20.35)	33.83 ( $\pm$ 17.02)	34.37 ( $\pm$ 15.11)	F = 2.74 p = .08		.08
	Emotional well-being (%)	39 *	41 *	41 *	$\chi^2$ = 2.13 p = .34		t1-t2: r = .05 t1-t3: r = .02 t2-t3: r = .15
	Stigma (%)	22 *	25 *	25 *	$\chi^2$ = .46 p = .79		t1-t2: r = .04 t1-t3: r = .02 t2-t3: r = .11
	Social support (%)	12 *	16 *	16 *	$\chi^2$ = .45 p = .79		t1-t2: r = .01 t1-t3: r = .02 t2-t3: r = .02
	Cognition (%)	31.33 ( $\pm$ 18.83)	30.23 ( $\pm$ 15.46)	25.50 ( $\pm$ 14.29)	F = 5.47 p = .00	t1-t3: p = .02 t2-t3: p = .01	.15
	Com. (%)	25 *	29 *	25 *	$\chi^2$ = 3.24 p = .19		t1-t2: r = .19 t1-t3: r = .01 t2-t3: r = .02
	Bodily discomfort (%)	39 *	41 *	34 *	$\chi^2$ = 13.41 p = .00	t1-t2: p = .00 t1-t3: p = .00	t1-t2: r = .45 t1-t3: r = .45 t2-t3: r = .04
	Summary index (%)	31.73 ( $\pm$ 10.94)	32.47 ( $\pm$ 10.33)	31.50 ( $\pm$ 9.75)	F = .71 p = .45		.02
FES-I		35.00 ( $\pm$ 10.91)	34.90 ( $\pm$ 10.93)	34.38 ( $\pm$ 10.44)	F = .37 p = .60		.01
BBS		46 *	48 *	49 *	$\chi^2$ = 41.73 p = .00	t1-t2: p = .00 t1-t3: p = .00	t1-t2: r = .58 t1-t3: r = .59 t2-t3: r = .07
TUG (seconds)		11.5 *	11 *	11 *	$\chi^2$ = 30.05 p = .00	t1-t2: p = .00 t1-t3: p = .00	t1-t2: r = .52 t1-t3: r = .53 t2-t3: r = .19
2MWT	Walking distance (metres)	82.53 ( $\pm$ 27.72)	81.91 ( $\pm$ 30.37)	85.98 ( $\pm$ 28.48)	F = 1.50 p = .23		.04
Spirometry	FVC (%)	93.90 ( $\pm$ 19.48)	95.00 ( $\pm$ 19.78)	96.30 ( $\pm$ 18.02)	F = 2.49 p = .10		.07
	FEV <sub>1</sub> (%)	94.45 ( $\pm$ 21.75)	96.28 ( $\pm$ 22.37)	96.86 ( $\pm$ 20.78)	F = 3.81 p = .51		.11
	FEV <sub>1</sub> / FVC (%)	96 *	97.5 *	98 *	$\chi^2$ = 1.07 p = .58		t1-t2: r = .09 t1-t3: r = .10 t2-t3: r = .09
	IVC (%)	82.55 ( $\pm$ 16.48)	80.93 ( $\pm$ 15.29)	82.60 ( $\pm$ 14.89)	F = 3.94 p = .03	t2-t3: p = .00	.12

\* median (for non-parametric data)

Abbreviations. 2MWT: two-minute walk test; ADL: activities of daily living; BBS: Berg Balance Scale; Com.: communication; FES-I: Fall Efficacy Scale-International; FEV<sub>1</sub>: forced expiratory volume in the first second; FVC: forced vital capacity; HADS: Hospital and Anxiety Depression Scale; IVC: inspiratory vital capacity; PDQ-39: Parkinson's disease Questionnaire-39; SD: standard deviation; T1: pre-intervention; T2: post-intervention; T3: follow-up; TUG: Timed Up and Go.

## 9.6. Score differences and minimum clinically important difference (MCID)

The score differences of the outcomes -within and between the study groups- from baseline to follow-up- were compared with the MCID values for each instrument, to detect any clinically significant change within the group or difference between the groups. The MCID values for each measurement tool have already been reported in Sections 8.7.1-8.7.15. However, table 9.11 summarises the MCIDs values for the measurement tools of the present study, and the population for which they were calculated.

**Table 9.11.** MCIDs values for the measurement tools and the population for which they were calculated.

Measurement tool		MCID value	Population	References for the MCID values
HADS	HADS-A	1.5	Chronic obstructive pulmonary disease (inpatients)	Puhan et al., 2008
	HADS-D	1.5	Chronic obstructive pulmonary disease (inpatients)	Puhan et al., 2008
PDQ-39	PDQ-39 SI (%)	4.2	Parkinson's disease	Horváth et al., 2017
BBS		3	Multiple sclerosis (inpatients and outpatients)	Gervasoni et al., 2017
FES-I		3.5	Geriatric population	Delbaere et al., 2010
TUG (in seconds)		3.4	Lumbar degenerative disc disease (after surgery)	Gautschi et al., 2017
2MWT	2MWD (in metres)	5.5	Chronic obstructive pulmonary disease	Johnston et al., 2017
Spirometry	FVC% (%)	3	Respiratory disorders	Kafaja et al., 2017
	FEV <sub>1</sub> (%)	5	Chronic obstructive pulmonary disease	Jones et al., 2014

Abbreviations. 2MWD: two-minute walking distance; 2MWT: 2-metre walk test; BBS: Berg Balance Scale; FES-I: Fall Efficacy Scale-International; FEV<sub>1</sub>: forced expiratory volume in the first second; FVC: forced vital capacity; HADS: Hospital and Anxiety Depression Scale; HADS-A: Hospital and Anxiety Depression Scale-anxiety; HADS-D: Hospital and Anxiety Depression Scale-depression; MCID: minimal clinically important difference; PDQ-39: Parkinson's disease Questionnaire-39; SI: summary index; TUG: Timed Up and Go.

### 9.6.1. Between-groups score differences

Table 9.12 presents the between-group comparison at baseline, post-intervention and follow-up. Clinically significant differences between the study groups were detected only at post-intervention for the following outcomes: 2MWD ( $11.56 > 5.5$ ), FVC (%) ( $4.05 > 3$ ).

**Table 9.12.** Score differences between the study groups at baseline, post-intervention, follow-up.

Variables	T1: $\Delta$ (IG-CG)	T2: $\Delta$ (IG-CG)	T3: $\Delta$ (IG-CG)
HADS-A	0.65	-1.22	-0.66
HADS-D	-0.37	-1.45	-0.87
PDQ-39 SI (%)	3.33	-2.09	0.81
BBS	-0.03	2.19	1.18
FES-I	2.67	-0.12	0.39
TUG (in seconds)	-1.11	-2.47	-2.13
2MWD (in metres)	3.07	11.56 *	5.38
FVC (%)	0.72	4.05 *	1.79
FEV <sub>1</sub> (%)	-2.22	0.42	-0.32

\* clinically significant changes

Abbreviations. 2MWT: two-minute walking distance;  $\Delta$ : difference; BBS: Berg Balance Scale; CG: comparison group; FES-I: Fall Efficacy Scale-International; FEV<sub>1</sub>: forced expiratory volume in the first second; FVC: forced vital capacity; HADS-A: Hospital and Anxiety Depression Scale-anxiety; HADS-D: Hospital and Anxiety Depression Scale-depression; IG: intervention group; PDQ-39 SI: Parkinson's disease Questionnaire- 39 summary index; T1: pre-intervention; T2: post-intervention; T3: follow-up; TUG: Timed Up and Go.

### 9.6.2. Within-group score differences

Table 9.13 (p. 231) shows that within the IG, the following clinically significant changes occurred:

- HADS-A ( $2.07 > 1.5$ ), PDQ-39 summary index (SI) ( $4.68 > 4.2$ ), BBS ( $4.85 > 3$ ), 2MWD ( $7.40 > 5.5$ ), and FVC (%) ( $4.1 > 3$ ) from baseline to post-intervention.
- BBS ( $3.94 > 3$ ), and FVC ( $3.47 > 3$ ) from baseline to follow-up.

On the contrary, no clinically significant changes emerged within the CG from baseline to follow-up (table 9.14, p. 223).

**Table 9.13.** Score changes within the IG.

Variables	T1	T2	T3	$\Delta$ (T2 –T1)	$\Delta$ (T3 –T1)	$\Delta$ (T3 –T2)
HADS-A	8.88	6.81	7.47	-2.07 *	-1.41	0.66
HADS-D	10.5	9.22	9.66	-1.28	-0.84	0.44
PDQ-39 SI (%)	35.06	30.38	32.31	-4.68 *	-2.75	1.93
BBS	43.87	48.72	47.81	4.85 *	3.94 *	-0.91
FES-I	37.80	35.57	35.33	-2.23	-2.47	-0.24
TUG (in seconds)	13.15	11.03	11.32	-2.12	-1.83	0.29
2MWD (in metres)	85.02	92.42	90.20	7.40 *	5.18 *	-2.16
FVC (%)	94.62	98.72	98.09	4.1 *	3.47	-0.63
FEV <sub>1</sub> (%)	90.57	95.23	94.90	4.66	4.33	-0.33

\* clinically significant changes

Abbreviations. 2MWT: two-minute walking distance;  $\Delta$ : difference; BBS: Berg Balance Scale; FES-I: Fall Efficacy Scale-International; FEV<sub>1</sub>: forced expiratory volume in the first second; FVC: forced vital capacity; HADS-A: Hospital and Anxiety Depression Scale-anxiety; HADS-D: Hospital and Anxiety Depression Scale-depression; PDQ-39 SI: Parkinson's disease Questionnaire- 39 summary index; T1: pre-intervention; T2: post-intervention; T3: follow-up; TUG: Timed Up and Go.

**Table 9.14.** Score changes within the CG.

Variables	T1	T2	T3	$\Delta$ (T2 –T1)	$\Delta$ (T3 –T1)	$\Delta$ (T3 –T2)
HADS-A	8.23	8.03	8.13	-0.2	-0.1	0.1
HADS-D	10.87	10.67	10.53	-0.2	-0.34	-0.14
PDQ-39 SI (%)	31.73	32.47	31.5	0.74	-0.23	-0.97
BBS	43.9	46.53	46.63	2.63	2.73	0.1
FES-I	35.27	35.53	34.80	0.26	-0.47	-0.43
TUG (in seconds)	14.26	13.5	13.45	-0.76	-0.81	-0.05
2MWD (in metres)	82.05	81.61	85.63	-0.44	3.58	4.02
FVC (%)	93.9	94.67	96.3	0.77	2.4	1.64
FEV <sub>1</sub> (%)	93.63	96.17	96.63	2.54	3	0.46

Abbreviations. 2MWT: two-minute walking distance;  $\Delta$ : difference; BBS: Berg Balance Scale; FES-I: Fall Efficacy Scale-International; FEV<sub>1</sub>: forced expiratory volume in the first second; FVC: forced vital capacity; HADS-A: Hospital and Anxiety Depression Scale-anxiety; HADS-D: Hospital and Anxiety Depression Scale-depression; PDQ-39 SI: Parkinson's disease Questionnaire- 39 summary index; T1: pre-intervention; T2: post-intervention; T3: follow-up; TUG: Timed Up and Go.

## 9.7. Categorisation of anxiety and depression severity

A further within- and between-group analysis for anxiety and depression was carried out. The scoring of each sub-scale (HADS-A, HADS-D) for each participant, was replaced by the corresponding category (table 9.15), as had been proposed by Zigmond and Snaith (1983) (Appendix 8.8). As seen in the table, at baseline none of the participants was identified as not depressed in order to meet all the inclusion criteria of the RCT (section 8.5.2). The majority of participants (n= 38, 61.3%) were classified as 'mild depressed', whereas only five subjects (8%) as 'severe depressed'. At the end of the intervention period, 15.32% of subjects in the IG and 13.33% in the CG were free of depression. Regarding anxiety, 28 subjects (45.1%) were free of anxiety at baseline, whereas 31 (50%) at post-intervention and follow-up assessment.

**Table 9.15.** Categorisation of anxiety and depression based on the HADS-A and HADS-D scores.

Categories for anxiety and depression		Pre-intervention		Post-intervention		Follow-up	
		IG (n= 32)	CG (n= 30)	IG (n= 32)	CG (n= 30)	IG (n= 32)	CG (n= 30)
Normal (0-7)	A	15	13	18	13	18	13
	D	0	0	5	4	5	1
Mild (8-10)	A	7	10	10	11	9	10
	D	20	18	23	12	21	17
Moderate (11-14)	A	5	7	3	6	4	7
	D	9	10	2	10	3	10
Severe (15-21)	A	5	0	1	0	1	0
	D	3	2	2	4	3	2

Acronyms. A: anxiety; CG: comparison group; D: depression; IG: intervention group; n: number of patients.

## 9.8. Correlations of anxiety and depression with other variables

### 9.8.1. Correlation of anxiety and depression at baseline (whole sample)

A correlation analysis was conducted at baseline for the whole sample to explore the strength of relationship of anxiety and depression with: the anthropometric characteristics, features related to PD and rest outcome measures (table 9.16, p. 234). The results revealed a medium correlation between anxiety (as measured by the HADS-A subscale) and



depression (as measured the by the HADS-D subscale) ( $r_s = .36$ ,  $p = .00$ ), with higher levels of depression being associated with higher levels of anxiety.

With respect to depression, there was not any strong correlation ( $r/r_s = .50-1.00$ ) between the HADS-D subscale and the other examined variables. However, there was a medium correlation ( $r/r_s = .30- .49$ ) between depression and: several domains of QoL (PDQ-39 mobility, PDQ-39 ADL, PDQ-39 emotional well-being, PDQ-39 cognition), PDQ-39 SI score, FOF (FES-I), functional mobility (TUG test), balance (BBS), and exercise tolerance (2MWT). In particular, higher levels of depression were associated with: poorer QoL, more FOF to perform ADLs, more time to complete the TUG test, lower levels of functional balance, and less walking distance covered in two minutes time. Lastly, its correlation with the other variables was either small ( $r/r_s = .10-.29$ ) or very small ( $r/r_s = .00-.09$ ).

Concerning anxiety, there was only a strong correlation ( $r/r_s = .50-1.00$ ) between the HADS-A and PDQ-39 cognition subscale. The tests also indicated medium correlation ( $r/r_s = .30-.49$ ) between anxiety and: some subscales of QoL (PDQ-39 mobility, PDQ-39 emotional well-being, PDQ-39 bodily discomfort), and QOL (as measured by the PDQ-39 SI). The correlation between anxiety and the other variables was either small ( $r/r_s = .10-.29$ ) or very small ( $r/r_s = .00-.09$ ).

**Table 9.16.** Correlation of anxiety and depression with other variables at baseline.

Variables		Anxiety	Depression
Gender		$r_s = .26$ $p = .03$	$r_s = .15$ $p = .23$
Age (in years)		$r = -.08$ $p = .95$	$r_s = .22$ $p = .08$
Years since PD diagnosis		$r_s = .09$ $p = .45$	$r_s = -.02$ $p = .84$
H&Y stage		$r = .16$ $p = .21$	$r_s = .26$ $p = .03$
FOG		$r_s = .21$ $p = .91$	$r_s = -.01$ $p = .08$
UPDRS	Total	$r_s = .06$ $p = .63$	$r_s = .23$ $p = .07$
	III (motor)	$r_s = .08$ $p = .53$	$r_s = .27$ $p = .03$
HADS	Anxiety		$r_s = .36$ $p = .00$
	Depression	$r_s = .36$ $p = .00$	
PDQ-39	Mobility	$r = .30$ $p = .01$	$r_s = .35$ $p = .00$
	ADL	$r_s = .21$ $p = .10$	$r_s = .32$ $p = .01$
	Emotional well-being	$r_s = .37$ $p = .00$	$r_s = .32$ $p = .01$
	Stigma	$r_s = .06$ $p = .63$	$r_s = .18$ $p = .15$
	Social support	$r_s = .09$ $p = .47$	$r_s = .11$ $p = .40$
	Cognition	$r = .57^*$ $p = .00$	$r_s = .31$ $p = .01$
	Communication	$r_s = .20$ $p = .11$	$r_s = .22$ $p = .08$
	Bodily discomfort	$r_s = .38$ $p = .00$	$r_s = .10$ $p = .44$
	Summary index	$r = .48$ $p = .00$	$r_s = .45$ $p = .00$
FES-I		$r = .29$ $p = .02$	$r_s = .32$ $p = .01$
BBS		$r_s = -.18$ $p = .15$	$r_s = -.47$ $p = .00$
TUG		$r_s = .13$ $p = .32$	$r_s = .40$ $p = .00$
2MWT	Walking distance	$r = -.13$ $p = .32$	$r_s = -.41$ $p = .00$
Spirometry	FVC %	$r_s = -.23$ $p = .07$	$r_s = -.06$ $p = .63$
	FEV <sub>1</sub> %	$r_s = -.06$ $p = .64$	$r_s = .02$ $p = .84$
	FEV <sub>1</sub> / FVC %	$r_s = .18$ $p = .17$	$r_s = -.06$ $p = .60$
	IVC %	$r = -.22$ $p = .08$	$r_s = -.08$ $p = .50$

\* strong relationship

Acronyms. 2MWT: two-minute walk test; ADL: activities of daily living; BBS: Berg Balance Scale; H&Y: Hoehn and Yahr; FES-I: Fall Efficacy Scale-International; FOG: freezing of gait; FEV<sub>1</sub>: forced expiratory volume in the first second; FVC: forced vital capacity; HADS: Hospital and Anxiety Depression Scale; IVC: inspiratory vital capacity; PDQ-39: Parkinson's disease Questionnaire-39; TUG: Timed Up and Go.

### 9.8.2. Correlation of depression at post-intervention and follow-up (intervention group)

As the levels of depression were statistically significant improved in the IG at post-intervention and follow-up; it was decided to conduct a correlation analysis to explore the strength of the linear relationship between depression (as measured by the HADS-D) and the secondary outcome measures, using Spearman rho (Table 9.17, p. 236). As seen in the table, at post-intervention there was a strong relationship ( $r_s = .50-1.00$ ) between the HADS-D and: HADS, PDQ-39 mobility and FES-I scores; and a medium relationship ( $r_s = .30-.49$ ) between the HADS-D and: HADS-A, PDQ-39 emotional well-being, PDQ-39 social support, PDQ-39 SI, BBS, FVC, FEV<sub>1</sub>, and FEV<sub>1</sub>/FVC. At follow-up, a strong relationship ( $r_s = .50-1.00$ ) was found between HADS-D and: HADS, PDQ-39 mobility, and PDQ-39 emotional well-being. Lastly, a medium relationship ( $r_s = .30-.49$ ) was detected between HADS-D and: PDQ-39 social support, PDQ-39 SI, FES-I, BBS, and FEV<sub>1</sub>/FVC scores.

**Table 9.17.** Correlation of depression (HADS-D) with other outcomes at post-intervention and follow-up for the IG.

Variables		Post-intervention	Follow-up
HADS	Anxiety	$r_s = .34$ $p = .05$	$r_s = .29$ $p = .10$
	Total	$r_s = .67^*$ $p = .00$	$r_s = .84^*$ $p = .00$
PDQ-39	Mobility	$r_s = .58^*$ $p = .00$	$r_s = .50^*$ $p = .00$
	ADL	$r_s = .20$ $p = .26$	$r_s = .21$ $p = .23$
	Emotional well-being	$r_s = .34$ $p = .05$	$r_s = .55^*$ $p = .00$
	Stigma	$r_s = .03$ $p = .85$	$r_s = .08$ $p = .62$
	Social support	$r_s = .33$ $p = .05$	$r_s = .35$ $p = .04$
	Cognition	$r_s = .25$ $p = .15$	$r_s = .26$ $p = .13$
	Communication	$r_s = .05$ $p = .75$	$r_s = -.18$ $p = .30$
	Bodily discomfort	$r_s = .16$ $p = .34$	$r_s = .21$ $p = .23$
	Summary index	$r_s = .45$ $p = .00$	$r_s = .42$ $p = .01$
FES-I		$r_s = .52^*$ $p = .00$	$r_s = .41$ $p = .01$
BBS		$r_s = -.47$ $p = .06$	$r_s = -.45$ $p = .00$
TUG		$r_s = .17$ $p = .33$	$r_s = .23$ $p = .19$
2MWT	Walking distance	$r_s = .23$ $p = .20$	$r_s = -.25$ $p = .15$
Spirometry	FVC %	$r_s = -.35$ $p = .06$	$r_s = -.23$ $p = .20$
	FEV <sub>1</sub> %	$r_s = -.32$ $p = .06$	$r_s = -.28$ $p = .11$
	FEV <sub>1</sub> / FVC %	$r_s = -.37$ $p = .03$	$r_s = -.33$ $p = .06$
	IVC %	$r_s = -.09$ $p = .60$	$r_s = -.06$ $p = .73$

\* strong relationship

Acronyms. 2MWT: two-minute walk test; ADL: activities of daily living; BBS: Berg Balance Scale; FES-I: Fall Efficacy Scale-International; FEV<sub>1</sub>: forced expiratory volume in the first second; FVC: forced vital capacity; HADS: Hospital and Anxiety Depression Scale; IVC: inspiratory vital capacity; PDQ-39: Parkinson's disease Questionnaire-39; TUG: Timed Up and Go.

## 9.9. Falls

### 9.9.1. Number of falls and fallers

During the five-month study period, a total of 121 falls were reported by 28 participants (45.1%); 12 of them being in the IG and 16 in the CG. The majority of falls were recorded in the CG (n= 65, 53.7%); compared the IG (n= 55, 46.7%). Nine participants fell once; whereas 19 were classified as recurrent fallers, reporting at least two falls during the whole study period. The majority of fallers (n=18) were at H&Y stage three; whereas one at H&Y stage 1.5; five at H&Y stage two, and four at H&Y stage 2.5.

### 9.9.2. Predictors of falls

With respect to the fallers during the intervention and follow-up period, the logistic regression contained one dependent variable (fallers), and seven independent variables, related to the demographic characteristics and features of the disease (gender, age, years since PD diagnosis, walking aid, UPDRS, H&Y stage, FOG). The full model containing all the predictors was statistically significant ( $\chi^2 = 16.97$ ,  $p = .01$ ), indicating that the model was able to distinguish between patients who reported and did not report any fall, and correctly classified 74.2% of cases. However, only two independent variables made a unique statistically significant contribution to the model ( $p < .05$ ): the UPDRS total score and H&Y stage. The strongest predictor of reporting falls was H&Y stage ( $p < .03$ ). An increase in these two independent variables resulted in an increased probability for a fall.

### 9.9.3. Circumstances of falls

The circumstances of falls were fully reported in 116 out of 121 cases, and are presented in table 9.18 (p. 239). A large proportion of falls (n= 39, 32.2%) occurred in the late night or early in the morning (12 am – 9 am). In addition, the majority of falls happened at patient's home/property (n= 69, 57%). Seven occurred indoors, but not in patient's home; and 44 outdoors. The living room was the most common location for indoor home/property falls and for overall falls (n= 28, 23.1%). Four home/property falls occurred outdoors (balcony, garden). The activity during fall was reported in 115 cases. Ambulation (n= 79, 65.3%),

standing (n= 27, 22.3%) and transfers (n= 10, 7.2%) activities indicated that the cause of falls was related to static or dynamic balance. An interesting fact is that four falls occurred at late night, when the patients woke up to go to the toilet. The fall-associated factors were reported in 75 falls (61.5%). The number of intrinsic (n= 37) and extrinsic factors (n= 38) was almost equal; whereas in four cases the subjects were unable to describe the fall's cause, as they were found suddenly on the floor. Two common extrinsic factors (pavements and beach) are related to the landscape of the country. In particular, the subjects reported that they lost their balance while walking on a sandy or rocky beach. In addition, the bad condition of pavements (i.e. broken pavements), obstacles -especially on narrow pavements (i.e. parked cars, trees, stairs leading to front doors)-, and uphill/downhill pavements, led to 27 outdoors falls.

**Table 9.18.** Circumstances of falls during the intervention and follow-up period.

Variables			Number of cases
Time	Morning (5:00 am - 11:59 am)		44 (36.3%)
	Afternoon (12:00 pm – 3:59 pm)		12 (9.9%)
	Evening (4:00 pm – 7:59 pm)		37 (30.6%)
	Night (8:00 pm – 4:59 am)		22 (18.2%)
	Missing		6 (4.9%)
Location	Indoors		72 (59.5%)
	Outdoors		48 (39.7%)
	Missing		1 (0.8%)
Location for home/property	Indoors (n= 65)	Living room	28 (23.1%)
		Bedroom	12 (9.9%)
		Kitchen	8 (6.6%)
		Hallway	5 (4.1%)
		Bathroom	4 (3.3%)
		Stairs	3 (2.5%)
		Warehouse	3 (2.5%)
		Garage	1 (0.8%)
		Non-specified	1 (0.8%)
	Outdoors (n= 4)	Balcony	2 (1.6%)
		Garden	2 (1.6%)
Activity during fall	Ambulation (n= 79)	Walking	48 (39.7%)
		Turning	12 (9.9%)
		Stairs	7 (5.8%)
		Carrying	9 (7.4%)
		Running	3 (2.5%)
	Standing (n= 27)	Bend/reach	23 (19%)
		Shower	2 (1.6%)
		Dressing	1 (0.8%)
		Gardening	1 (0.8%)
	Transfers (n= 10)	To/from bed	2 (1.6%)
		To/ from chair/sofa	5 (4.1%)
		To/from car	1 (0.6%)
		Rolling out of bed	1 (0.6%)
Fall-associated factors	Intrinsic (n= 37)	Freezing	19 (15.7%)
		Loss of balance	9 (7.4%)
		Dizziness	4 (3.3%)
		Misjudgment	3 (2.5%)
		Distraction	2 (1.6%)
	Extrinsic (n= 38)	Pavement	27 (23.2%)
		Beach	5 (4.1%)
		Wet floor	3 (2.5%)
		Dark	2 (1.6%)
Work of medication during fall	Well		36 (29.7%)
	Moderate		53 (43.8%)
	OFF		25 (20.7%)

#### 9.9.4. Fall-related injuries

Of 121 falls, 32 (26.5%) sustained an injurious fall (table 9.19, p 240). Nearly 1/4 of injurious falls (n= 9) occurred indoors. In 15 cases, more than one injury was reported. Medical/ healthcare assistance was required in 14 cases. In seven cases, the patients sought assistance from a local pharmacy. In Greece, it is very common for employees working in

pharmacies to provide first aids, in case of minor injuries. The injuries were not serious, there was no fracture, and no need for hospitalisation. However, two lacerations required sutures.

**Table 9.19.** Features of injuries during the intervention and follow-up period.

Variables		Number of cases
Injury due to fall	No	89
	Yes	32
Type of injury	Pain	21
	Contusion	16
	Laceration	13
	Ligament lesion (hand finger)	1
Medical /healthcare assistance	No	18
	Hospital	5
	Doctor	2
	Pharmacy	7

### 9.10. Satisfaction questionnaire

Twenty two participants –ten males and twelve females- of the IG completed the SQ about the exercise classes. However, only in twelve cases all the questions were answered. The feedback of participants was positive, indicating subjective improvements in emotional well-being and mobility. Although the questions were just designed for the exercise programme, few answers provided useful information for the educational programme. The emergent themes were related to the questionnaire's items. A synopsis of the answers of items one to eight is presented in table 9.20 (p. 241).



**Table 9.20.** Answers of questions 1-8.

Question	Answers	Number of answers
1. How easy/hard was the programme?	Moderate	7
	Easy with some difficulties, tailored in PD	6
	Quite easy	5
	Easy	2
	Difficult	2
2. Have you noticed any positive effects from doing the programme?	Improvements in gait parameters	7
	Improvements in emotional well-being	5
	Improvements in transfers	4
	More erected posture	4
	General improvements	3
	Social interaction	2
	Improvements in reaching	1
	Improvements in breathing	1
	More knowledge about PD	1
3. Have you noticed any negative effects from doing the programme?	No	17
4. What did you like more about the programme?	Whole programme	11
	Physiotherapy team	3
	Breathing exercises	2
	Group-based design	2
	Gait training	2
	Ball exercises	1
	Variety of exercises	1
5. What did you like less about the programme?	Nothing	8
	Exercise venue	4
	Few exercise bouts	2
	No variety of exercises	2
	Ball exercises	1
	Breathing exercises	1
6. What would you like to change in the programme? Any ideas to propose?	No changes	7
	More exercise hours	6
	Exercise venue	4
	Time of exercise (evening instead of morning)	1
	More homogeneous sample: similar age and level of mobility	1
	Warmer indoor exercise environment	1
7. What motivated you to participate to the programme?	To improve functional mobility	7
	Financial reasons	5
	Socialisation- meet other patients with PD	2
	The programme was provided by specialists in PD	2
	Family's instigation	1
	To improve knowledge about PD	1
8. What motivated you to complete the programme?	Health improvement related to PD	13
	Physiotherapy's team attitude	4
	Socialisation	3
	Knowledge about PD	2
	Group-based environment	1
	Variety of exercise modalities	1

Acronyms. PD: Parkinson's disease.

*How easy/hard was the programme?*

The participants characterised the exercise programme passable, whereas only two found it difficult. Only six individuals gave long answers, describing the programme generally easy with some difficulties, tailored in PD population. One female wrote: *"I cannot say how much easy or difficult the training programme was, as its aim was to exercise PD patients."* (GA05). Although, some patients found the programme difficult at the beginning, they did not quit: *"...Some exercises were difficult, but I didn't give up!"* (AE07); *"During the first sessions I found the whole programme difficult. I was getting tired easily. Afterwards, the fatigue was reduced."* (PE01).

*Have you noticed any positive effects from doing the programme?*

Twenty out of 21 participants found the exercise programme beneficial. Although the patients were asked to specify the positive effects they noticed, three of them reported just *"General improvements"* (AE18, IL10, PE01). A large proportion (n= 10) noticed improvements in functional mobility: transfers and quality aspects of gait. Some beneficial effects on mobility were obvious even during the first weeks of exercise: *"Many movements were improved from the first week."* (IL03). Regarding walking, one respondent noticed improvements (increased step length, walking speed and improved balance) both in indoor and outdoor walking. An interesting fact was that in many cases the verb 'learning' was written in the answers. This may indicate that the whole programme helped the patients to see the exercise as a learning procedure to manage PD and change their lifestyle: *"I learned practical exercises that helped my walking and my sitting on a chair."* (GA05); *"...I learned how to overcome freezing and turn safely."* (PF04); *"I learned to stand up properly and correct my posture."* (PE01); *"I learned how to perform stretches by myself."* (GA03); *"I learned to use my belly to breathe."* (AE21); and *"The exercise and educational sessions helped me to learn more about my disease."* (PF12). In addition, five patients reported improvements in emotional well-being: *"I was feeling better psychologically!"* (GA05); *"Wellness"* (PF06). Lastly, two patients pointed out the social interaction of group therapeutic exercise programmes between individuals with similar features: *"I made new friends."* (IL10); *"I met other people with Parkinson's disease."* (IL05).

*Have you noticed any negative effects from doing the programme?*

None of the trainees found the exercise harmful. Indicatively, one female wrote: *“No negative effects, just positive!”* (IL10).

*What did you like more about the programme?*

With respect to what they liked more about the programme, few patients gave specific answers; whereas 11 individuals reported that they enjoyed the whole programme. It seems that exercise instructors specialised in PD, polite, and having the knowledge how to approach the participants; it was not only appreciated by the patients, but it was also an important factor to complete the programme: *“Our physiotherapist taught us all the exercises in detail. He explained the aim of each exercise and answered all our questions relevant to the exercise.”* (IL01); *“The physiotherapists were polite...they were correcting our movements, if they were wrong.”* (GA05); *“The physiotherapist’s instructions were clear...”* (PE01). Similarly, a non-monotonous design, consisting of a variety of exercise modalities, both attracted the participants, and motivated them to complete the programme. The group-based design also enhanced sociability and reduced isolation: *“...I was arriving half an hour earlier to discuss with my friends”* (PF04); *“In group exercise programmes you can meet and compare yourself with other patients. You learn many things from them...how to address daily problems related to Parkinson’s.”* (IL03).

*What did you like less about the programme?*

Eight out of 15 patients, who responded this question, found nothing negative for the programme: *“Everything was perfect!”* (PE09). Only five individuals expressed some complaints about the design of the training programme. Two wrote that the total training hours were not enough, and more exercises could be included into the programme. However, in two municipalities there were complaints about the exercise venues, as they were considered either small for the current training protocol or dirty.

*What would you like to change in the programme? Any ideas to propose?*

The participants were generally satisfied: *"I would not change anything"* (IL10); *"The programme was effective."* (AE21); *"....I was totally satisfied."* (PE09). However, some modifications were proposed. Some of them were related to their responses on question five (What thing did you like less about the programme?), about the exercise venue and the total training hours (i.e. three exercise bouts a week). One respondent proposed outdoors exercise, because: *"...the weather in Athens is perfect for training outdoors."* (PF05). Lastly, despite that the air temperature in the venues was strictly followed the recommendations in the literature, one female would prefer exercise in warmer environment, as she was feeling cold.

*What motivated you to participate in the programme?*

The reasons, which led the individuals to participate in the study, were not related to the primary aim of the study (depression); despite the potential participants were aware of it. The main reason was to improve functional mobility (n= 7): ADLs and walking. An interesting fact, related to the ongoing financial crisis in Greece, was that five patients decided to participate, due to their inability to cover the expenditures of a physiotherapy programme. Specifically, one respondent wrote: *"PD is the disease of the rich people. Visits to doctors, physiotherapists and speech therapists are very expensive. I cannot afford the high cost, as my income has been reduced."* (PF12). Two people decided to participate in the programme, because it was offered by healthcare professionals with knowledge in PD; indicating the need for specialised physiotherapists in PD in Greece. One female wrote that: *"This study is provided by a doctoral student and healthcare professionals, under the supervision of the Greek PD Association. Thus, they are specialised in the management of the disease."* (PF06). Another patient wrote: *"The programme was provided by physiotherapists with knowledge in PD. There are no many physiotherapists and doctors specialised in PD (in Greece)...."* (AE21).

*What motivated you to complete the programme?*

Improvements mainly in motor function and emotional well-being motivated patients to complete the programme. 13 individuals decided to complete the programme, due to improvements in gait (n= 6), ADLs (n= 3), emotional well-being (n= 3), breathing (n= 1). One male wrote: *"The improvement on my gait, posture and psychology."* (GA09). Additional factors were: the physiotherapists' attitude, and the interaction with other people suffering from PD. Lastly, it is believed that previously reported answers in the question "What did you like more about the programme?" may provide additional reasons that led the individuals to complete the intervention.

*Do you have anything else you would like to add?*

Eighteen patients completed the last question providing more information about their perception relevant to the exercise programme and their emotional well-being. It is remarkable that nobody wrote negative comments, whereas some included a thankful statement: *"Thank you for the exercise programme. I was lucky I participated"* (AE14). Some patients described the programme as one of their few pleasures: *"Apart from food, the programme was my only pleasure."* (AE03); *"...I live alone and I feel lonely...I was very happy on Wednesdays and Fridays.....I made new friends.....After the end of the exercise bout, we were going out for coffee"* (IL05). Four patients with PD expressed their desire, to participate in similar programmes in the future: *"It would be great if Epikouros-kinisi will offer a similar free exercise programme"* (PE12); *"I want to follow again the exercise programme in the autumn"* (IL05).

Five patients wrote comments related to their psychological well-being. One woman stated the motivation needed when treating depressed population: *"Sometimes, due to depression, it was difficult to take the decision to get out of my house and go to the exercise venue.....I was feeling exhausted for no reason...The programme gave me motivation... When I was starting the exercise, I was able to complete the whole session"* (PF06). Two patients explained the reason that their psychological well-being was not improved at the end of the intervention period. It seems that their family did not support them: *'My*

*psychology was not improved. My husband does not support me. We do nothing together. He pressures me to walk faster. When the tremor starts, he hits my hand....” (AE13); “My psychology is getting worse. I am afraid of my disease. When I walk, I feel that all the people watch at me.... My mother always tells me that I am suffering from PD and I ‘m gonna die. I feel depressed. I cannot do the activities I did in the past...” (AE21). Finally two patients expressed their concern about the future: “I am worried about the future. I live by myself” (IL05); “Although the programme was beneficial, the fear of falling has been increased. I am afraid of a future fall, because Mrs X had a fall-related injury.” (PE09).*

### 9.11. Summary of Chapter 9

- There were no significant differences at baseline between the study groups in all the socio-demographic characteristics and health status; apart from the UPDRS-I scores.
- There were no significant differences between the two groups at baseline, end of treatment or follow-up on any outcome measure score, apart from the HADS score at post-intervention.
- The IG demonstrated a statistically significant improvement in depression (HADS-D), anxiety (HADS-A), psychological distress (HADS), QoL (PDQ-39) functional balance (BBS), functional mobility (TUG), exercise tolerance (2MWT) and lung function (FVC, FEV<sub>1</sub>) scores at the end of the treatment. These improvements, apart from the QoL, persisted up to the end of the three-month follow-up period.
- On the contrary, in the CG, only the BBS and TUG scores were statistically significant improved from baseline to post intervention and follow-up.
- However, the between-group comparison revealed that there were no significant differences between the IG and CG at post-intervention and follow-up, apart from the HADS total score at post-intervention.
- The group-based exercise and educational programme also resulted in clinically significant changes (based on the MCID values) on HADS-A, PDQ-39 SI, BBS, 2MWD and FVC scores at the end of the treatment. However, only the MCID value for PDQ-39 has been established in PD.
- Although the SQ was completed only by 22 participants of the IG; the feedback was positive, indicating subjective improvements in emotional well-being and mobility.

- The drop-out rate for the entire period of study in both groups was 13.3%, and the training protocols were not harmful for the participants.
- 121 falls were recorded during the entire study's period. The majority of falls occurred at patient's home/property; and they were caused by both intrinsic and extrinsic factors. Only ¼ of them caused minor injuries.

# **CHAPTER 10**

## **RCT – DISCUSSION**



### 10.1. Main findings – summary of key results

The main purpose of the present RCT was to deliver and investigate the short- and longer-term effects of an eight-week group-based therapeutic exercise and educational programme in patients with PD suffering from depression; against a CG, which followed a home-based, individualised, unsupervised training. Depression, as measured by the HADS-D, was the primary endpoint of the study; whereas anxiety, QoL, functional mobility, exercise tolerance, balance, FOF, lung function and patients' satisfaction about the group-based exercise programme the secondary outcomes. The number of falls and their features through the whole study period, were also recorded.

The results of the study, contrary to the researcher's expectation, demonstrated no statistically significant differences ( $p > .05$ ) between the two study groups for the primary and secondary outcomes at the end of the treatment and three-month follow-up period, whereas the effect sizes were small (eta squared= 0.01- 0.05;  $r = .10-.29$ ). A significant difference ( $p = .03$ ) was only detected for the total HADS scores at post-intervention, where the improvement was significant higher in the IG, and the magnitude of the difference between the groups was medium (eta squared= .07).

However, regarding the within-group comparison; the findings suggest that a supervised group-based exercise and educational programme was able to elicit positive responses in a relatively short time frame. In particular, the data extraction showed significant improvements ( $p \leq .05$ ) for the primary and secondary outcomes, with medium and large effect sizes (partial eta squared  $\geq .06$ ;  $r \geq .30$ ), at the end of the treatment. Only the FES-I, FEV<sub>1</sub>/FVC and IVC scores were not significantly improved ( $p > .05$ ). The positive findings were also supported by the trainees' feedback in the SQ; who reported subjective improvements in emotional well-being, mobility and lung function, due to the training. Although after the end of the intervention period, the vast majority of the measured values had the tendency to return to the initial levels prior the exercise. the results remained statistically significant improved, apart from the PDQ-39 SI scores. Lastly, with respect to the CG, no statistically significant results emerged in all the outcomes –apart from the BBS

and TUG scores-, as a result of the home-based individualised training. However, the vast majority of values appeared to improve from baseline to follow-up.

## **10.2. Interpretation of findings**

### 10.2.1. Baseline characteristics

The study groups were similar at baseline regarding almost all: the anthropometric and socio-demographic characteristics; the health status, including the severity of the disease; and the key and secondary outcomes. It seems that the proper randomisation procedure and the concealed allocation reduced the possibilities for selection bias, and any difference between the two study groups at baseline reflects chance (Moher et al., 2010). The vast majority of anthropometric and socio-demographic characteristics, and health status (i.e. gender, age, nationality, marital status, education level, years since PD diagnosis, medical comorbidities) were consistent with the results of the present survey. Thus, the interpretation of these findings is presented in the survey's discussion (sections 7.2.1 and 7.2.2).

#### *Anthropometric characteristics*

Concerning the anthropometric characteristics, a finding of particular interest was that the mean BMI of participants was 28.11 kg/m<sup>2</sup>, and the vast majority of subjects (82.2%) were overweight and obese. This is in contrast with prior work indicating that the BMI of patients with PD is usually normal (18.6-24.9 kg/m<sup>2</sup>), and less than that of the controls (van de Marck et al., 2012). This may be explained by the fact that PD patients usually lose weight, due to the combination of non-motor (i.e. dysphagia, loss of sense of smell and taste), and motor symptoms, which may increase energy expenditure (Kashikara, 2006). Furthermore, a nationwide study that was held in Greece revealed that the mean BMI of Greek adults was 26.5 kg/m<sup>2</sup>, and that the BMI of 57.7% of the population was more than 25 kg/m<sup>2</sup> (Kapantais et al., 2012). Surprisingly, in the present study the mean BMI value for the whole sample was higher (28.11 kg/m<sup>2</sup>). However, it is unknown whether the participants lost weight since PD diagnosis, as this was not an objective of the current study. In addition, it

is doubtful whether the BMI is a strong indicator of body fat, because the equation for the calculation of BMI is not able to capture the proportion in fat and fat-free body mass (van de Marck et al., 2012).

#### *Health status- Parkinson's disease*

Despite the increasing recognition of therapeutic exercise in PD management from the early stages, in order to educate patients and minimise the future impacts of the disease (Keus et al., 2013), the majority of participants (41.9%) were in the middle stage of the disease (H&Y stage three). As depression in PD does not correlate with the stage of motor deficits (Marsh, 2013), and the majority of patients in Greece start physiotherapy in the middle stages of the disease -when the motor symptoms and the impacts of PD are more apparent-; this reveals concerns whether Greek population with early PD is well informed about the disease, co-morbidity depression, and the role of physiotherapy against the disease progression.

Regarding freezers' proportion, 21% of the overall sample was detected as freezers using the Snijders and Bloem FOG Test. This proportion was much lower compared to that of a recent study, which classified 54.3% of its sample (H&Y stage one to four) as freezers, based on item three of the FOG Questionnaire (Amboni et al., 2015). However, the FOG Questionnaire assesses the severity of FOG, and does not utilise clinimetric tools to distinguish freezing and non-freezing population (Shine et al., 2012). On the contrary, the Snijders and Bloem FOG Test is not a 'gold standard' to detect freezers. Furthermore, the test was not performed during the 'off-state', as it is proposed in the literature (Snijders et al., 2012), probably limiting the freezers' proportion. Only the method of observation could reveal the exact number of freezers, which is rarely possible in the clinical setting and research field. Thus, the classification of freezers and non-freezers is usually based on self-reported data (Nieuwboer and Giladi, 2013).

Lastly, all the participants were under antiparkinsonian medication. L-dopa was administered to the vast majority (93.5%) of patients, as it is the most common used drug for the management of motor symptomatology (Heisters, 2011). Despite the fact that monotherapy is a recommended pharmacological treatment in the early stages of the disease (H&Y stage one to two), and two drug-therapy in the moderate and advanced stages (H&Y stage three to five) (NICE, 2006; Rao et al., 2006); one-drug therapy was administrated only to 19.3% of the sample. This is quite interesting, as 58.1% of the population was classified in the early stages of the disease (H&Y stages 1-2.5) by a specialist neurologist in PD. Further investigation was beyond the scope of the current thesis, but future studies should examine whether neurologists in Greece have the adequate knowledge to assess PD population and treat them with the most effective drugs.

#### *Health status- depression*

Although all the participants were identified as depressed by the HADS-D ( $\text{HADS-D} \geq 8$ ), only 37.1% of them had been officially diagnosed with depression, either before or after PD diagnosis. A possible explanation might stem from the fact that depression in PD is often under-recognised (section 3.6.4). Moreover, the HADS-D is not a recommended tool for the diagnosis of depression in PD. As the estimated rates of depression in PD appear much higher when rating scales with cut-off values are used, instead of specific diagnostic criteria (Reijnders et al., 2008), some subjects of the sample may have not been suffering from MDD. If a cut-off of 11 (indicating clinical depression) instead of eight (borderline for depression) (Zigmond and Snaith, 1983), had been selected, the percentage of participants with clinical diagnosis of depression may have been higher.

The HADS subscales also revealed that the co-existence of anxiety and depression ( $\text{HADS-A} \geq 8$  and  $\text{HADS-D} \geq 8$ ) in 53.2% of the whole sample. This percentage is lower to that supported in the literature, varying from 67% to 76%, when the DSM criteria are used (Chen and Marsh, 2014). The high co-existence may be explained by the fact that anxiety and depression share common pathophysiological mechanisms (Section 3.6.2) (Kano et al., 2011). However, a direct comparison between present findings and prior work may not be

feasible, as the HADS subscales are not the 'gold standards' for the diagnosis of mental disorders. In addition, the HADS-A includes only items relevant to GAD and fear, excluding symptoms of other anxiety disorders (Leentjens et al., 2008). This limitation of the HADS-A, in combination with the fact that the minimum score on the HADS-D subscale was eight; may partly explain the medium positive relationship ( $r_s = .36$ ) of anxiety and depression at baseline for the whole sample.

With respect to depression's treatment, 19 out of 23 patients diagnosed with MDD –either by a psychologist or medical doctor- were under antidepressant medication. This proportion (82.6%) is much higher in comparison to the evidence supporting that less than 50% of overall clinically depressed population in PD receive any type of treatment (e.g. drugs, CBT) (Aarsland et al., 2011). In addition, 16 out of 25 patients, who received antidepressant treatment, were females. However, in PD, women are more likely to receive antidepressant regardless of behavioural symptoms, as they are more likely to seek mental health treatment than men (Miller and Gronin-Golomb, 2010). With reference to the whole sample, 30.6% (19 out of 62) of patients were treated with antidepressant drugs. Surprisingly, this percentage is lower compared to the findings of a nationwide study in Greece, which revealed that 37.1% of Greek patients with PD were under drug treatment for depression (Konitsiotis et al., 2014).

A highly unexpected finding was that six patients, non-diagnosed with MDD, were receiving antidepressant drugs. However, it is unsure whether all of them gave accurate responses about their mental health. Perhaps, they hidden a clinical diagnosis of depression during the screening procedure. Even in nowadays, there is still the stigma of having a mental disorder in Greece, especially among senior population, and in rural areas. However, they were aware of the purpose of the current investigation through the 'Patient Information Sheet'. In addition, based on empirical knowledge and discussing with two neurologists working in Athens; it is quite common for neurologists in Greece to administer to patients antidepressant medication when depressive symptoms are recognised, without clinical

diagnosis by psychologists, using accurate diagnostic criteria for mental disorders, as “....*Parkinson and depression usually coexist.*”.

#### *Relationship of anxiety and depression with other variables at baseline*

The relationship of anxiety and depression with the anthropometric characteristics, features of PD, mobility, QoL and lung function; revealed that mental disorders in PD are a complex concept, and a combination of factors may be responsible for the increased levels of depression. Indeed, the Pearson Correlation co-efficient detected only one strong relationship ( $r = .50-1.00$ ) between anxiety scores (HADS-A) and cognition, as measured by the PDQ-39 cognition subscale; whereas all the other correlations varied from very small to medium ( $r/r_s \leq .49$ ). However, caution is needed for the interpretation of the results for three reasons. Firstly, all the patients scored at least eight in the HADS-D, based on the eligibility criteria. Secondly, the HADS-A contains only items relevant to GAD and panic disorder. Thirdly, all the patients were in the first three stages of the disease (H&Y stage one to three).

The small and medium correlations of anxiety and depression with H&Y staging, mobility and age (Section 9.8.1) may be explained by the fact that depression and anxiety may occur at any stage of PD and affect all the ages. High rates of depression at early stages, may indicate a reactive depression, due to PD diagnosis; whereas increased rates at advanced stages may be associated with the more severe symptoms (e.g. motor fluctuations) and impacts of the disease (Marsh, 2013). Similarly, GAD and panic disorder in the first stages and younger ages are related to disruptions in the professional domain and financial impacts; whereas in later stages, to motor fluctuations, FOG and perceived disability (Nuti et al., 2004; Pontone et al., 2009). The medium correlations between anxiety and depression and QoL (as measured by the PDQ-39 SI) (Section 9.8.1) may reflect the fact that in spite of QoL being a subjective complex concept, anxiety and depression are among the main predictors of diminished QoL in PD (Hanna and Cronin-Colomb, 2012; Den Oudsten et al., 2017). However, the relationship of anxiety with QoL in PD has been less studied (Hanna and Cronin-Golomb, 2012). Regarding, the PDQ-39 subscales, more

evidence is required to support whether the non-motor symptoms of PD –such as cognitive impairments or symptoms that cause bodily discomfort- may influence anxiety and depression levels (Marsh, 2013; Dissanayaka et al., 2014).

The current results are partly consistent with findings from previous literature in PD. Similarly to the present study, Rojo et al. (2003) and Quelhas and Costa (2009) found small and medium correlations between anxiety and depression levels and: H&Y stage, years since PD diagnosis, and total UPDRS score. Although the results of two trials support a medium correlation between anxiety, depression and overall QoL (Quelhas and Costa, 2009; Jones et al., 2015); the study by Hanna and Cronin-Golomb (2012) found a strong correlation. Concerning the secondary outcomes of the present study related to mobility (i.e. BBS, TUG test, 2MWT), no relevant trial was identified. Previous work only examined the prevalence of depression in the motor subtypes of PD. Three studies concluded that the highest rates of depression appear with the postural instability-gait disturbances subtype (Riedel et al., 2010; Dissanayaka et al., 2011; Djamshidian, and Friedman, 2014), whereas van der Hoek et al. (2011) supported that the prevalence of depression is similar between the motor subtypes of PD. Lastly, although in the present study the correlation between gender and depression was found small ( $r_s = .15$ ); prior work supports that levels of depression are more elevated in women (Rojo et al., 2003; Riedel et al., 2010), because they are more likely than men to respond positively to the items of self-rated scales of depression (Allen-Burge et al., 1994).

#### 10.2.2. Primary outcome-depression

Contrary to the author's expectation and the bulk of the literature, depression scores did not significantly differ ( $p > .05$ ) between the two groups at the end of the treatment and follow-up, confirming the null hypothesis for the primary outcome measure (Section 8.2.4). However, the within-group comparison of both groups revealed that only the treatment of the IG was effective ( $p = .00$ ), and superior to that of the CG to relieve depressive symptoms at the end of the treatment. Although the depressive scores in the IG started to increase at the end of the intervention, to reach the initial levels prior intervention, the results

remained significantly improved ( $p = .01$ ) from the baseline up to the end of the three-month follow-up period. The effect sizes in both cases revealed that the magnitude of the effect was medium ( $r = .30 - .49$ ).

On the contrary, the MCID for the HADS-D revealed no clinically significant differences between and within the study groups. However, the author was not aware of the MCID value for the HADS-D in patients with PD or other neurological disorders, such as MS. Thus, the MCID in inpatient population with COPD (Puhan et al., 2008) was selected to identify any changes in the clinical intervention. The comparison between this MCID value and the difference in means may have been inaccurate, because the MCID score is specific to the population being studied and is non-transferable across patient populations. In addition, even in a specific population, the lack of a universally accepted methodology to determine the MCID score, results in a wide range of MCID values for a single outcome measure (Wright et al., 2012).

The statistically significant improvements within the IG are of particular interest, due to the time that the current study was conducted in Greece (March 2015-March 2016). Although strict eligibility criteria (Sections 8.5.2 and 8.5.3) aimed to minimise the effects of pharmacological and non-pharmacological treatment on the study's results, the events that occurred that period in the country, which were not part of the intervention, may have affected the study outcome, threatening the internal validity of the study (Buckwalter et al., 2009). In particular, on 29<sup>th</sup> June 2015, during the intervention period or the post-intervention assessment in three municipalities, capital controls were introduced, and a referendum took place on 5<sup>th</sup> July 2015 to decide whether Greece was to accept the bailout conditions proposed by Troika. Despite the fact that there was danger that these events may have had a serious impact on the emotional well-being of participants, introducing bias to study's results and preventing any improvement in the HADS-D scores, the treatment for the IG was proved effective.



Based on the above data, it is believed that the systematic design of the intervention plan -that aimed to select the appropriate exercise parameters and design an interdisciplinary education component- may have been responsible for the significant improvements at post-intervention and follow-up. The possible reasons that both components of the programme produced antidepressant effects in the IG, are reported and analysed in the following paragraphs. However, as the therapeutic exercise classes were combined with education, it is not possible to know the extent to which each component contributed to the effective outcome of the treatment. Although the investigation of the underlying mechanism, responsible for the significant improvements, was beyond the scope of the present thesis; it is believed that both biological and psychological mechanisms, proposed in the literature, may have contributed to the antidepressant effects. These mechanisms have probably worked in a complex and combined way for the reduction of depressive symptoms (Craft and Perna, 2004).

With respect to exercise classes, evidence-based data in PD and depressed population were combined for the selection of the appropriate exercise parameters, in order to improve both the primary and secondary outcomes of the study. This was a crucial step, as the evidence to relieve depression in PD is limited, and is provided mainly by studies that assessed depression as a secondary outcome in a non-depressed population.

Firstly, the high supervision in the IG may have produced antidepressant effects. Although a meta-analysis in depressed population, concluded that both supervised and unsupervised formats were associated with antidepressant effects, evidence was provided mainly by supervised programmes (Schuch et al., 2016a). Supervised programmes may have motivational effects in trainees and improve long-term exercise behaviour, when they are led by experienced staff (Schuch et al., 2011). Indeed, in the present study, the motivation the subjects received by the exercise instructors, was reported in the SQ. It was also cited that the exercise instructors explained the aim of all the exercises, which were included in the programme, and taught patients to perform them by themselves by giving them guidance.

The group exercise format may have also provided some mental benefits. According to the 'social interaction hypothesis', the group-based exercise leads to improved opportunities for social interaction between the trainees and pleasure; which, in turn, may have beneficial effects on mental health (Ransford, 1982). Thus, Keus et al. (2007) recommend a group training protocol in PD population to improve emotional well-being. Enhanced sociability leading to new friendships, and reduced isolation due to the group format, were also reported by four participants in the SQ. However, recent studies in depressed population failed to demonstrate any evidence about the superiority of group programmes compared to individualised training. It is believed that other factors, such as the mode of exercise and the exercise intensity, may play a more significant role (Wegner et al., 2014).

In addition, it seems that the selected exercise dose may have been adequate in order to alleviate depressive symptoms. In particular, two one-hour exercise sessions were performed for a total period of eighth weeks, plus 150 minutes of walking per week. These are the minimum recommended parameters for exercise in depressed population (CPG, 2008; Ravindran et al., 2009). The systematic review by Stanton and Reaburn (2014), based on effective RCTs in depressed population, proposed the range of exercise dose to manage depression in the overall population, and calculated the means for each exercise parameter; confirming that both the total length of intervention and exercise frequency of the present study were suitable to relieve depression, but below the means (mean intervention period: 9.3 weeks; and mean exercise frequency: 3.8 times a week). On the contrary, the duration of each exercise session was beyond the normal range (30-40 minutes). However, this information was derived from studies using solely aerobic exercise as intervention. Furthermore, although the mechanism of action is unknown, it seems that more training hours and interventions longer than ten weeks, do not display greater antidepressant effects (Rethorst et al., 2009). Lastly, the findings about the intensity of aerobic and anaerobic exercise are controversial, and it seems that both moderate and high intensity (Appendix 4.5) may produce antidepressant effects (Stanton and Reaburn, 2014). However, a high intensity was avoided in the present study, as it may produce fatigue, a prevalent non-motor symptom of PD (Keus et al., 2013).

It is unknown whether the combined aerobic and anaerobic protocol contributed to significant improvements in depression scores at the end of the treatment. In depressed population, evidence is mainly derived from aerobic training; whereas anaerobic, and mixed programmes combining aerobic and anaerobic exercises, have been less studied. In addition, resistance training programmes have been briefly described; and major exercise parameters –such as the number of repetitions, the length of rest period, and the load of resistance- were not reported in the protocol of previous trials in depressed population (Kvam et al., 2016). Although there is limited and controversial evidence, it seems that resistance training, similarly to aerobic exercise, induces the expression of growth factors, such as the brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF), promoting neurogenesis in the hippocampus, whose volume is reduced in MDD (Phillips, 2017). However, in the current study, relevant blood tests to measure the expression of the BDNF or VEGF before and after the intervention, as well as magnetic resonance imaging (MRI) for the measurement of brain volumes, were not performed. Thus, the underlying biological mechanisms that may have been responsible for the antidepressant effects of exercise were not explored.

Concerning the educational classes, they may have provoked antidepressant effects through the education of participants about PD and ways to overcome the daily difficulties arising from the symptoms and signs of the disease. Education is a suggested strategy to improve the management of depression in primary care (Unützer and Park, 2012). The systematic review by Cuijpers et al. (2009) concluded that psychoeducational treatment, providing by psychologists and additional professionals, was effective in treating depression, producing similar effects as other psychological approaches, such as CBT.

Lastly, the positive influences of exercise in the secondary outcomes of the study, may have improved depressive status. Although the pathophysiology of depression in PD is complex, it seems that motor restrictions and disability may contribute in a degree to the development of mental disorders (Marsh, 2013). Thus, it is possible that the statistically significant improvements ( $p \leq .05$ ) in the secondary outcomes of mobility, resulted in

significant reductions on depression scores at post-intervention. Previous studies, which explored the effects of therapeutic exercise in PD, found significant improvements both in depression and motor function at the end of the treatment (Nadeau et al., 2010; Smania et al., 2010; Cugusi et al., 2015; Hashimoto et al., 2015). Nevertheless, only Smania et al. (2010) hypothesised that the improvements on depression may have been due to the increased confidence in balance and reduced number of falls. This may be interpreted by the 'self-efficacy theory', which supports that the ability of the individual to perform an exercise programme successfully increases confidence, and is strongly related to changes in behaviour (Bandura, 1977). Similarly, the 'mastery hypothesis' supports that the performance of a challenging pursuit, such as exercise, may create a sense of independence and success (Boggiano et al., 1982).

Despite the psychological mechanisms that were reported above, in the IG of the present study, the relationship between the HADS-D and BBS scores at post-intervention and follow-up were medium ( $r_s = .30-.49$ ), and between HADS-D and TUG and 2MWT scores small ( $r_s = .10-.29$ ). However, the tests did not examine the relationship between the improvements in depression and mobility. Thus, it cannot be supported that the increased sense of self-empowerment produced significant antidepressant effects. In addition, a tool to assess the self-efficacy –such as the Self-Efficacy for Exercise (SEE) Scale or SEE Questionnaire- or self-confidence – such as the Activities-specific Balance Confidence Scale (ABCS)- before and after treatment was not used. Thus, it was not possible to explore the relationship between improved depressive symptoms (as measured by the HADS-D) and self-efficacy (as measured by the SEE Scale or Questionnaire) or self-confidence scores (as measured by the ABCS), and support or reject the 'self-efficacy' theory. This was beyond the scope of the current project, and the author was not aware if the SEE Scale, SEE Questionnaire and ABCS have been translated and validated in the Greek language.

The failure of the CG to improve depression through the whole study period, probably stems from the design of the intervention for the CG. Although the selected dose of exercise could relieve depression (Stanton and Reaburn, 2014), and the exercises were

similar to that of the IG; it is believed that due to the lack of supervision, the members of the CG received less motivation for the performance of the programme. Despite the fact they received specific information and guidelines on how to use the booklet and perform the exercises by themselves; the selection of specific exercises was based on their own judgment, and no further advice was given through the weekly telephone calls. Moreover, as the programme was individualised, they were more isolated, and had no benefit from social interactions with other participants. However, a SQ, similar to that of the IG was not delivered to the members of the CG. Hence, the personal beliefs of the subjects about the intervention were not recorded in order to interpret the less antidepressant effects.

In addition, caution is needed for the results' interpretation within the CG, based on the 'self-efficacy' or 'mastery hypothesis'. The study by Smania et al. (2010) revealed that significant improvements in depression (as measured by the GDS) were accompanied by improvements in self-confidence (as measured by the ABCS) and motor function (as measured by the BBS), in PD patients who followed an individualised training programme, supporting the 'self-efficacy' theory for the antidepressant findings. On the contrary, in the present study, despite the fact that some aspects of mobility (BBS, TUG scores) were improved significantly at the end of intervention and follow-up, probably they did not lead to increased confidence and improvements in the mental domain, similar to that of the IG. However, none relevant measurement tool was used to assess the self-efficacy or confidence levels at baseline and at the end of the intervention period.

Thereby, based on the lack of supervision and social interaction in the CG; and assuming that almost the same exercises were performed in both programmes, and the exercise intensity was not well-defined; the 'reductio ad absurdum' principle leads to support that the significant antidepressant effects in the IG were almost related to the socialisation aspects of group-based exercise, and the motivation the participants received by the exercise instructors and lecturers. On the contrary there is less evidence to support other predominant psychological mechanisms, which could relieve depression; such as the 'self-efficacy theory', the 'mastery hypothesis', and the 'distraction hypothesis', which claims

that diversion from unpleasant stimuli -due to exercise- may lead to improved mood (Paluska and Schwenk, 2000).

With respect to the biological mechanisms, the degree of their interaction with the 'social interaction hypothesis' to produce antidepressant effects in the IG, is unknown. A considerable body of research supports that exercise could relieve depressive symptoms through the increased of the synaptic transmission of monoamines (monoamine hypothesis), the increased levels of  $\beta$ -endorphins during exercise (endorphin hypothesis), the expression of growth factors BDNF and VEGF in several brain areas (neurogenesis hypothesis), the reduced activity of the HPA axis and decreased secretion of glucocorticoids, and the regulation for the production of inflammatory cytokines that have been shown to be dysregulated in depressed people. Concerning the overall depressed population, this information is mainly derived from studies utilising aerobic exercise, whereas anaerobic training has been less studied. In addition, there is limited evidence for the action of these mechanisms under different doses of exercise (e.g. total training period, exercise intensity) (Wegner et al., 2014). However, in the present RCT, the lack of physiological tests before and after the treatment, did not allow us to explore the precise biological mechanisms, responsible for the antidepressant effect in the IG.

The current research not only it demonstrated that depressed patients with PD obtained antidepressant benefits in relevant short time from commencing a well-designed, group-based, supervised exercise, combined with educational classes; but also that the significant results did remain up to the end of a three-month follow-up period. This is in contrast with the follow-up data in depressed population, which indicate that the effects of exercise diminish after the end of the intervention (Kvam et al., 2016). Interestingly, the systematic review by Whiteford et al. (2012) concluded that when there is no treatment in the follow-up period the depressive levels return to their initial values within one year after the end of the exercise in 53% of cases. Although the responsible aetiological mechanism for this decline is unknown, it seems that the high BDNF synthesis stops after the end of the

exercise programme, preventing further improvement in depressive scores (Knaepen et al., 2010).

Regarding the present study, the follow-up period had a small duration of three months. Perhaps if the follow-up period was longer (i.e. one year), the significant improvements in depression would not be long-lasting. Indeed, the scores started to increase from the post-intervention to the follow-up assessment. In addition, similarly to the study by Hoffman et al. (2011), the IG followed a self-reported exercise during the follow-up period, which may partly explain the significant results up to the follow-up assessment. Interestingly, during the follow-up period, the IG followed the same individualised, unsupervised, home-based exercise programme as the CG. So it may be inaccurate to assume that the exercise dose was optimum to maintain the effect. It seems that the group exercise programme that preceded, motivated the participants to continue the exercise. In addition, the fact that they were taught by the instructors how to perform the exercises correctly, may have facilitated them to follow the exercises as being described in the booklet.

#### *Comparison with previous studies*

The findings of the present study on depression scores were partly in congruence with those obtained from previous trials in patients with PD. In those trials the intervention was either exercise or education; or a combined programme. The main privilege of the present study, compared to those, is that it was the first that assessed the effectiveness of an exercise programme, combined with education, in PD population with clinical levels of depression. However, it should be pointed out that during the writing period of the current thesis, one year after the completion of the RCT's intervention, one study (Sajatovic et al., 2017) with similar design was published. In addition, only the present project aimed to explore both statistical and clinical changes due to intervention, report the effect sizes and participants' satisfaction; apart from two studies (Smania et al. 2010; Sajatovic et al., 2017)

The literature search identified only two studies, in which supervised multimodal exercise was combined with education; in order to reduce scores of depression in PD, either as a primary (Sajatovic et al. 2017) or secondary outcome (Dereli and Yaliman, 2010). Both of them revealed significant improvements in depression scores at the end of the intervention, whereas their total PEDro score was four (fair quality), indicating that their results were believable. However, as only in the trial by Sajatovic et al. (2017) depression was assessed as principal outcome, similarly to the present study, its design aimed to alleviate depressive symptoms. In addition, the study population was only PD patients diagnosed with MDD, using the MADRS (Sajatovic et al. 2017). With respect to the study by Dereli and Yaliman (2010), the BDI was selected to assess depression and the subjects could be non-clinically depressed at baseline. However, the MADRS is considered superior to the self-report questionnaires (e.g. BDI, HADS-D) for screening depression in PD, and is a highly recommended tool (Section 8.7.1).

The subjects in the study by Sajatovic et al. (2017) were allocated either to a supervised, combined group or self-guided exercise and chronic disease self-management programme; which is a behavioural intervention, including educational classes, aiming to reduce the negative consequences of chronic somatic diseases. Similarly to the present study, aerobic and resistance training were combined; whereas in both groups, three one-hour exercise bouts were performed for 12 consecutive weeks. Although the randomisation procedure and the clinician-rated MADRS ensured less possibilities for selection and assessor bias respectively; the trial lacked an intention-to-treat analysis and between-group comparisons of the results at post-intervention and follow-up. Instead, a combined sample was included in the data analysis, making impossible to know the group that was favoured more due to intervention. However, the results demonstrated significant changes in depressive scores from baseline up to the end of the 12-week intervention and 12-week follow-up period for the combined group. The benefits were also confirmed by the participants' satisfaction. In contrast to the current project, their study aimed to explore the mechanisms that may have been responsible for the relief of depression. Plasma analysis revealed that the levels of Interleukin 6 (IL-6) cytokine and BDNF remained stable through the whole study period; whereas the quality of sleep -using the Scales for



Outcomes in PD-Sleep Scale (SCOPA-S)- and the self-efficacy –as measured by the General Self-Efficacy Scale-, improved significantly. Thereby, contrary to the literature, only the psychological mechanisms were proved effective to alleviate depression in PD.

Concerning the study by Dereli and Yaliman (2010), patients were allocated either to a physiotherapist-supervised or an unsupervised home group. The exercise programme in both groups was performed three times a week for 10 weeks. Although the QoL was the primary aim of the study; similarly to our findings, patients in the supervised physiotherapy group benefited more, and the underlying mechanisms for the antidepressive effects were not explored. In addition, the long-term effects were not assessed. The lack of randomisation is one of the basic limitations of the study, as there are increased possibilities for selection bias. Lastly, due to the lack of sample size determination, the statistic power may have been small; hence, the treatment effect may have been overestimated.

Furthermore, one additional trial (Trend et al., 2002) was detected, which investigated the short-term effectiveness of intensive multidisciplinary approach for people with PD and their carers. The participants attended a day care unit one day per week for six consecutive weeks. Each weekly session lasted 5.5 hours. It combined group-based and individualised treatment, based on individual needs; and consisted of exercise by a physiotherapist, education by a specialist PD nurse, occupational therapy and speech and language therapy. Although a direct comparison between the findings of the present RCT with those of the study by Trend et al. (2002), may not be feasible, due to the different study design; the significant improvements in depression, as measured by the HADS-D in such a short time, may indicate that multidisciplinary programmes may encourage greater improvements in depressive levels, than combined exercise and education classes. However, clinical levels of depression were not among the eligibility criteria, and the study lacked a control or comparison arm in order to define the superiority of this approach over other treatment or usual care.

As already recalled in the present systematic review (Chapter 4); 15 RCTs were identified that assessed the effects of therapeutic exercise, as sole intervention, on levels of depression in patients with PD (Bridgewater and Sharpe, 1996; Burini et al., 2006; Schmitz-Hubsch et al., 2006; Modugno et al., 2010; Smania et al., 2010; Shulman et al., 2013; Nadeau et al., 2014; Cugusi et al., 2015; Dashtipour et al., 2015; Hashimoto et al., 2015; King et al., 2015; Rios Romenets et al., 2015; Schlenstedt et al., 2015; Sharma et al., 2015; Teixeira-Machado et al., 2015). Only six out of 15 studies found significant results at the end of the intervention (Appendix 4.6) (Smania et al., 2010; Nadeau et al., 2014; Cugusi et al., 2015; Hashimoto et al., 2015; King et al., 2015; Teixeira-Marchado et al., 2015). The effect size for depression was calculated only in the study by Smania et al. (2010), which revealed that the magnitude of the effect was large. Investigation of depression as primary measure is limited, apart from two trials, which revealed statistically significant improvements on depression at the end of the treatment (Cugusi et al., 2015; Teixeira-Marchado et al., 2015). Thus, the findings of the rest studies may reflect chance (Smania et al., 2010; Nadeau et al., 2014; Hashimoto et al., 2015; King et al., 2015). However, even in these studies (Cugusi et al., 2015; Teixeira-Marchado et al., 2015), depression was not the only primary outcome measure, as it is proposed by the CONSORT statement (Moher et al., 2010).

In contrast to the present RCT, none of the aforementioned 15 studies included solely patients with clinical levels of depression, using relevant rating scales with cut-off points. Hence, the findings of those RCTs with statistically significant results at post-intervention (Smania et al., 2010; Nadeau et al., 2014; Cugusi et al., 2015; Hashimoto et al., 2015; King et al., 2015; Teixeira-Marchado et al., 2015) are of particular interest; because it seems that exercise may reduce depressive symptoms in non-depressed population with PD. However, none of these studies aimed to explore the underlying mechanisms that produced antidepressant effects by using relevant tools. Only Smania et al. (2010) suggested that the 'self-efficacy theory' may partly explain the reduced levels of depression at the end of the treatment. However, as a supervised individualised format was selected by half of the trials (Smania et al., 2010; Nadeau et al., 2014; King et al., 2015), it seems that social support was not a strong predictor for antidepressant effects in PD patients that have completed the

treatment. Limited evidence is available for the longer-term effects of training, because only one trial with significant results at post-intervention (Smania et al., 2010) reported a follow-up assessment, four weeks after the end of the treatment. Surprisingly, contrary to our study and the bulk of the literature in depressed population (Whiteford et al., 2012) the improvements were not maintained in such a small timeframe.

Despite the fact the six effective studies (Smania et al., 2010; Nadeau et al., 2014; Cugusi et al., 2015; Hashimoto et al., 2015; King et al., 2015; Teixeira-Marchado et al., 2015) did not explore the mechanisms for the antidepressant effects, and it is unknown whether the design of the intervention aimed to relieve depression; based on the review by Stanton and Reaburn (2014), the exercise dose of these studies was optimum to achieve antidepressant effects. A direct comparison between the exercise parameters of our project and those trials is complicated; because there was a great variability among their parameters, as seen in Appendix 4.6. It is quite interesting that in three trials an individualised format was followed (Smania et al., 2010; Nadeau et al., 2014; King et al., 2015); as in the CG of the present study, which was not proved effective. Probably, the supervision of the training, in contrast to the present study, may have been a strong contributor for the significant results.

Lastly, with respect to the educational classes, few studies were identified that assessed the effects of education on depression in patients with PD (Macht et al., 2007; Tiihonen et al., 2008; Teixeira-Machado et al., 2015). These programmes aimed to improve the patients' knowledge on PD (Teixeira-Machado et al., 2015) or were focused on the socio-psychological aspects of the disease (Macht et al., 2007; Tiihonen et al., 2008). The RCT by Teixeira-Machado et al. (2015) compared the effectiveness of Feldenkrais exercise method (IG) with an educational programme (CG). The CG received education lectures once a week, for 24 weeks. The programme consisted of instructions to prevent falls, inform about the antiparkinsonian medication and manage the ADLs. The studies by Macht et al. (2007) and Tiihonen et al. (2008), lacked a comparison or control group; and the Edu-Park programme was applied, which was developed specifically for PD. It consisted of eight 90-minutes

supervised session, which were held once a week. The sessions aimed to inform patients about the psychological impacts of the disease and propose ways to manage them.

None of the aforementioned trials (Macht et al., 2007; Tiihonen et al., 2008; Teixeira-Machado et al., 2015) included participants with clinical levels of depression, depression was assessed as a secondary outcome, and the self-rating scales SDS (Macht et al., 2007; Tiihonen et al., 2008) and BDI (Teixeira-Machado et al., 2015) were selected to assess the effectiveness of the intervention. Despite the fact that the total hours of education were more than those in the present study (12 hours in the Edu-Park programme, 4 hours in the current project); the depressive scores were not improved at post-intervention. This is in contrast with the results of the present study. As in the present study the education was combined with exercise, in opposition to previous work, it seems that an education programme cannot by itself improve the depressed mood in PD. However, the content of educational classes in these trials differed from that of the present study.

### 10.2.3. Secondary outcomes

The results indicated no statistically significant changes regarding the secondary outcomes, between the two groups at the end of the treatment, apart from the total HADS scores, and at follow-up. Hence, the null hypothesis (section 8.2.4) cannot be rejected. This is quite interesting, because completing an exercise programme should have influenced more these variables in a positive manner, and it was expected that supervised training in a specialised exercise facility would have been more beneficial for physiological enhancements. However, the within-group comparison for the IG revealed statistically significant improvements ( $p \leq .05$ ) for almost all the secondary outcomes from baseline to post-intervention and follow-up, with usually a medium or large effect size (eta squared and partial eta squared  $\geq .06$ ;  $r \geq .30$ ). The results also highlighted that most outcomes had the tendency to return to the initial levels, after the end of the treatment. On the contrary, the CG did not show any significant improvement over time, apart from the BBS and TUG scores. This is quite encouraging, as it seems that an unsupervised, individualised, home-based programme could promote improvements in balance and functional mobility in a

relevant short timeframe. However, the fact that during the intervention period there was a more rapid and greater improvement in the outcomes for the participants that were allocated to the IG, reveals the superiority of the supervised group training.

It is noticeable that the use of MCIDs values revealed a few clinically significant changes in the IG. More precise; the HADS-A, PDQ-39 SI and 2MWD scores were significantly improved from baseline to post-intervention; and the BBS and FVC scores from baseline to follow-up. As the author was not aware if the MCID values have been calculated in patients with PD, apart from the PDQ-39 SI (section 9.6); in the current Section, the interpretation of the findings was based solely on the statistical tests, due to the reasons that have already been reported in Section 10.2.2.

Special caution is needed for the interpretation of the secondary outcomes. The sample size of the study was calculated only for the primary outcome. Hence, the statistical power for the secondary measures may have been low, preventing for drawing strong conclusions. Any difference may have been produced by chance (Freemantle, 2001). However, it seems that the dose of exercise was suitable to produce significant results, especially in the group-based training programme. This is not surprising, as the design of the exercise protocol focused in all the aspects of mild to moderate PD, synthesising relevant evidence-based data and recommendations. The fact that in the IG the vast majority of outcomes remained significantly improved up to the end of the follow-up period, may be explained by the length and the intervention of the follow-up period. In particular, the review by Mak et al. (2017) concluded that short exercise programmes in PD (up to 12 weeks) have beneficial effects on mobility for at least three months after the end of the treatment. In addition, in the present RCT, the subjects of the IG did not receive just usual care during the follow-up period, but participated in an unsupervised home-based exercise programme. Although, the members of the CG followed the same home-based programme through the whole study period (five months), they received less improvements. It seems that the training effect of the two-month group programme during the intervention period in the IG, was responsible for the significant findings up to the end of the three-month follow-up period.

Apart from the possible specific biological mechanisms, which are reported in the following sub-sections and may have contributed to the significant effects at mobility, the promotion of neuroplasticity<sup>23</sup> and neuroprotection<sup>24</sup> in PD through exercise may have played a significant role for the improvements in mobility (Ahlskog, 2011; Petzinger et al., 2013); but it was not explored using relevant clinical tests, because it was beyond the scope of the current project. This evidence is derived from neuroimaging studies in human beings and animal models studies; which have shown that aerobic, resistance and cueing training may have effects on neuroplasticity and neuroprotection. However, the relationship between animal studies, where a neurotoxin that destroys the DA neurons is administered, and PD in human beings, whose aetiology is unknown, is open to debate; as it is still unsure whether the exercise could have similar effects in specific brain areas. The same doubts appear in human studies that examine the neurobiological mechanisms of exercise in PD free population, as the action of exercise may differ in an already altered neurological system (Ahlskog, 2011).

More precise, and despite the controversial data, Exercise may mitigate the parkinsonian deficit by the increase of neurotrophic factors in the SN, such as the BDNF and glial-derived neurotrophic factor (GDNF), which regulate survival and activity of DA neurons and are reduced in PD. In particular, the increase of these factors has been thought to regulate branching and remodeling of axons and dendrites, whose length is reduced in PD. However, it is still unsure whether the neuron numbers within the circuit BG-cortex-thalamus could be also increased due to exercise (Ahlskog, 2011). In addition, increased blood flow in the brain and VEGF levels, whose expression in the SN of PD patients is also diminished, may provide angiogenesis, and in turn, facilitate neuroplasticity (Petzinger et al., 2013). Animal studies have shown that exercise-induced neuroplasticity may be achieved through the increase of DA neurotransmission, by enhancing the release of DA and increasing synaptic occupancy (Hirsch et al., 2016). Lastly, although there is no direct evidence for the neuroprotective effects of cueing training, it is believed that cues facilitate movements bypassing the affected BG, and activating further the premotor and parietal cortex for the

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<sup>23</sup> The capacity of the nervous system to develop new neuronal connections through life.

<sup>24</sup> The protection of the neuronal loss over time.

control of movements (van Wegen et al., 2014). Hence, based on these data, Mak et al. (2017) support that the long-term improvements following exercise training in PD population, are probably related to neuroplasticity.

Lastly, before the further interpretation of the secondary outcomes, it should be noted that regarding the HADS, only the findings of the two subscales (HADS-D and HADS-A) were interpreted. It is unsure whether the total HADS score is meaningful, because it is a measure of psychological distress among medical patients (Roberts et al., 2001). Psychological distress is a general term used by some practitioners to describe unpleasant feelings or emotions that impact the level of functioning (Ridner, 2004); it is not a syndrome as defined by the DSM or ICD criteria (Phillips, 2009); and individuals with psychological distress also experience symptoms of anxiety and depression (Ridner, 2004). On the contrary, anxiety and depression are narrow terms, and are included in the classification of mental disorders (Phillips, 2009). Thus, similarly to the present study, the vast majority of trials using the HADS scale have focused solely on its subscales (Roberts et al., 2001).

### *Anxiety*

The results indicated significant improvements in anxiety, as measured by the HADS-A, only in the IG from baseline to post-intervention ( $p = .00$ ), and from baseline to follow-up ( $p = .01$ ); whereas the magnitude of the relationship was large (partial eta squared = .31). Since there has been considerably less research examining the effect of exercise on anxiety in PD than depression, these results provide a useful addition to the current body of knowledge. In addition, the findings are of particular interest, as the intervention managed to relieve anxiety symptoms, despite the events that occurred in Greece during that time, and may have biased the results. Moreover, the findings provide evidence that a combined exercise and educational programme could decrease anxiety symptoms in an anxious free population with PD. Indeed, as anxiety was not one of the inclusion criteria of the present study; almost half of the participants were non-anxious at baseline. The current findings appear to conflict with previous studies in PD that suggested that therapeutic exercise itself (Dashtipour et al., 2015) or when combined with education (Sajatovic et al., 2017) did not

produce any anxiolytic effect. However, in both studies the data analysis was performed for the whole sample, and not for each study group separately.

A considerable body of research has proposed possible biological and psychological mechanisms for the anxiolytic effects of exercise, which are similar to those of depression. This is probably because anxiety and depression share common pathophysiological mechanisms for their onset and development. However, the mechanisms that connect exercise and anxiety are under debate (Wegner et al. 2017), because there is insufficient evidence about the anxiolytic effects of exercise in the overall population. Indeed, only 35% of experimental studies that have been included in reviews, managed to treat the symptoms of anxiety disorders (Bartley et al., 2013; de Souza Moura et al., 2015; Stonerock et al., 2015). Concerning the present RCT, it is believed that the mechanisms that produced antidepressant effects in the IG, as have been reported in Section 10.2.2, also reduced significantly the levels of anxiety. On the contrary, the non-significant improvement of depression in the CG may explain the ineffectiveness of the home-based programme to relieve anxiety symptoms.

### *Balance*

A significant increase ( $p \leq .05$ ) in balance abilities, as measured by the BBS, was observed in both groups over time. When comparing the two study groups to each other, effect size calculations indicated that no intervention was more effective at improving balance, as the effect sizes for the IG and CG were large ( $r \geq .50$ ). The findings are in line with prior work indicating that different types of physical activity (balance training, dance, Nordic walking) could improve significantly functional balance, as measured by the BBS, at the end of the treatment (Smania et al., 2010; Cugusi et al., 2015; Hashimoto et al., 2015) and at follow-up (Smania et al., 2010). Even training programmes with short intervention periods (seven weeks) could be effective (Smania et al. 2010).



The increased BBS scores may have been related to improvements in muscular strength of the leg muscles, and improved postural control. Evidence supports that the combination of balance and resistance training in PD is more effective on improving balance, compared with simple balance or resistance training programmes (Yitayeh and Teshome, 2016). In addition, balance training seems to be superior to walking on improving balance, because it is a more complex and dynamic task (Low et al., 2017). Hence, in the present study, probably the combination of muscle strengthening and balance training increased BBS scores in both groups.

Biological approaches support that resistance training improves muscle strengthening, due to alterations within the muscle cells and motor neurons supplying the muscle fibers. In particular, resistance training increases the muscle size, the number of motor units that are activated against the resistance, and the frequency of the nerve stimulation. Thus, agonist muscles are fully activated, whereas antagonist muscles are more relaxed (Glendinning and Enoka, 1994). In healthy individuals, these neural adaptations may take place within the first six weeks of training, before hypertrophy is seen (American College of Sports Medicine, 2009). Although, in an already altered neural system, as is found in PD, adaptations required for improvements in strength may be different to those of a healthy population; previous research suggests that PD patients commencing exercise, derive favourable alterations in muscle strength (Yitayeh and Teshome, 2016). However, in the present RCT, due to the shortage of equipment, the muscle strength was not assessed before and after the treatment. Lastly, the extent to which the stretches may have contributed to the relaxation of antagonist muscles remains unknown.

In addition, the progressive balance training of the present study may have improved postural control, through adaptations in neuromuscular control mechanisms. Balance relies on the ability of the peripheral sensory systems to react to the environment; and it requires vestibular, visual and proprioceptive feedback to and from the central nervous system, where the role of cerebellum is significant. The neuromuscular responses in the ankle and hip joints through balance training may decrease postural sway (Ruhe et al.,

2010). The progression of training from eyes opened to eyes closed conditions blocks the visual input; and the postural control relies solely on efferent neuromuscular and sensorimotor input, which could be improved with exercise (Low et al., 2017). Indeed, in the present study the education of the upright positioning of the head may have activated the proprioceptors in the neck, contributing to the normal body posture (Sakellari et al., 2005). In addition, the combination of balance and strength training may have improved the neuromuscular control in the ankle and hip joints.

Interestingly, despite the fact that the exercise booklet included less and more simple balance and strengthening exercises -for safety reasons-, and due to the shortage of relevant equipment; the supervised group-based environment was not proved superior to the unsupervised home-based programme to improve functional balance. This finding appear to contradict with the results of the systematic review by Lacroix et al. (2017), who concluded that supervised training interventions improved muscle strength, balance and walking distance to a greater extent than unsupervised programmes; because the performance of exercise was more precise in order to receive improvements, and the almost higher adherence rates in the supervised programmes resulted in greater exercise adaptations. Regarding the current study, possible explanations for the increased muscle strength in the CG include: the increased number of exercise sessions per week compared to the community-based programme, the clear instructions of the booklet accompanied by pictures, and the use of an exercise diary to record the exercise sessions. In addition, a privilege of unsupervised home-based programmes, which may have been responsible for the positive effects, is that participants were able to exercise at times that are most convenient to them. Lastly, it is possible that individuals who agree to participate in a research project may be more motivated to participate in all the study groups.

#### *Functional mobility and exercise tolerance*

Functional mobility, as measured by the TUG test, was statistically significant ( $p \leq .05$ ) improved in both groups over time; suggesting that both exercise programmes were able to elicit positive responses in a relatively short time frame. The effect sizes calculations

indicated that none programme was more effective at improving TUG scores, as all the effect sizes were large (partial eta squares  $\geq .14$ ;  $r \geq .50$ ). Regarding, the exercise tolerance, as measured by the 2MWT; the treatment favoured only the IG, from baseline to post-intervention and follow-up ( $p \leq .05$ ;  $r \geq .50$ ).

Improvements in the TUG test and 2MWT, indicated increases on walking speed, whereas both tests require muscle strength and balance (Podsiadlo and Richardson, 1991; Light et al., 1997). Thus, any improvement in the scores, may reflect increases in muscle strength and balance. Although the BBS indicated improvements in functional balance, the majority of its items assess static balance, whereas walking activities are excluded (Berg, 1988). It is unknown whether the gait training with the use of cues, the educational classes or the advice in the 'Individualised home-based exercise booklet', assisted patients to improve gait disturbances (i.e. FOG and festination), resulting in increased walking speeds. A gait analysis would have revealed any improvement in gait parameters; such as cadence, double support time and arm swing. In addition, as bradykinesia may be dependent on the emotional state of patients (Jankovic, 2008); perhaps any reduction in anxiety and depressive scores, may have improved the motor symptomatology, increasing the walking speed. Regarding the 2MWT, it is a submaximal test that could predict maximal aerobic capacity (Light et al., 1997). Based on the findings, it seems that the IG exhibited a greater training response due to the respiratory training and/or walking activity. This is quite interesting, as walking training was performed by both groups, under the same conditions; and therefore, aerobic fitness gains were expected for both groups. However, the intensity for the aerobic component was not monitored.

The current results for the group-based supervised programme are also supported by research examining functional mobility and exercise tolerance, using the TUG test and the 2MWT respectively, in the PD setting. In particular, supervised structured and unstructured training programmes, varying from seven to 12 weeks, have been proved effective in functional mobility at post-intervention (Cugusi et al., 2015; Hashimoto et al., 2015; Rios Romenets et al., 2015; Schlenstedt et al., 2015) and one-month follow-up period

(Schlenstedt et al., 2015). On the contrary, home-based programmes, either supervised or unsupervised, found trivial improvements in TUG scores (King et al., 2015; Rios Romenets et al., 2015); indicating that the findings of the present study regarding the CG, are of particular interest. Although the 2MWT has been rarely used in PD to assess exercise tolerance, one study found significant results following a six-month supervised resistance and aerobic training in a facility (Collett et al., 2017).

### *Fear of falling*

With respect to FOF, the results revealed trivial improvements ( $p \geq .05$ ) in both groups. The finding of the present study is dissimilar with previous research, illustrating that supervised exercise programmes up to 12 weeks long, may reduce FOF, as measured by the FES-I (Liao et al., 2015; Silva-Batista et al., 2018). However, these studies utilised more complex activities (Silva-Batista et al., 2018) or sophisticated equipment (Liao et al., 2015). Nevertheless, the results of the present RCT still surprising, because functional balance performance (BBS scores), which is important for the safe performance of many activities, was significantly improved. Interestingly, the mean BBS scores were over 41 from baseline to follow-up, indicating a low risk of falling (Keus et al., 2013); whereas the mean FES-I scores were above 23, indicating high fall concern (Delbaere et al., 2010). In addition, the mean TUG score at the end of the treatment, was less than 11.5 seconds, demonstrating less possibilities for falls in PD (Nocera et al., 2013). In turn, enhanced balance and functional mobility could increase confidence, reducing the FOF.

The fact that the FOF was not improved, reflects its complexity in PD. Studies support that greater FOF is associated with: the presence of hesitation and freezing, impaired balance, increased fall frequency, elevated levels of anxiety and depression, fatigue, middle-stage and advanced PD (Rahman et al., 2011; Lindholm et al., 2014), poorer stride length and gait speed (Bryant et al., 2011), and the presence of additional co-morbidities -such as osteoporosis, which may increase further the FOF- (Lindholm et al., 2014). Despite the fact that many of these factors were improved in both groups, the FES-I scores remained stable. However, it is unsure whether the community-based and the unsupervised home-based

environment were suitable for all the patients. Regarding the IG, the interaction with other patients may have increased FOF. Indeed, one female, whose balance was statistically and clinically significant improved at post-intervention, whereas FOF scores were slightly decreased; stated that her FOF was increased during the two-month intervention period, because some members of the group experienced falls and fall-related injuries.

### *Quality of life*

PDQ-39 SI reflected positive statistical responses ( $p = .00$ ) to the community-based exercise and education group from baseline to post-intervention, with a medium effect size ( $r = .33$ ). Nonetheless, that gain was completely reversed in the follow-up period. The statistically significant changes were also confirmed by the clinically significant changes from baseline to post-intervention, as the MCID value for the PDQ-39 in PD has been established (Horvath et al., 2017). With respect to the home-based group; neither the PDQ-39 SI score, nor the subscales' scores were improved due to the intervention, apart from the cognition and bodily discomfort subscales. Prior work showed that neither supervised or unsupervised, group or individual, facility or home-based exercise programmes, could improve PDQ-39 SI scores and PDQ-39 subscales' scores (Nadeau et al., 2014; Rios Romenets et al., 2015; Schlenstedt et al., 2015). Interestingly, improvements on mobility did not enhance QoL, whereas the non-relief of depressive symptoms in two trials (Rios Romenets et al., 2015; Schlenstedt et al., 2015) may have also contributed to insignificant results. Similarly to exercise, educational programmes in PD did not manage to detect any change in PDQ-39 scores, despite the fact that depressive symptoms were relieved (Mach et al., 2007; Tiihonen et al., 2008). However, none of the aforementioned studies consulted the MCID value to identify any clinical change over time.

QoL is a complex subjective concept (Opara et al., 2012), and is affected by a combination of factors. Although the primary motor symptoms, motor fluctuations and falls may affect QoL in PD (Rahman et al., 2008); it seems that non-motor symptoms are also strong predictors for diminished QoL (Rahman et al., 2008), and may have a greater impact on QoL than the motor symptoms (Martinez-Martin and Kurtis, 2012). The more number of non-

motor features, the more impaired QoL (Barone et al., 2009). Depression is the strongest predictive value for poor QoL in PD (Section 3.6.3), whereas additional non-motor symptoms (e.g. apathy, anxiety, FOF, and fatigue) are also consistent (Den Oudsten et al., 2007; Rahman et al., 2008). Lastly, some socio-demographic features (e.g. financial issues, unemployment) may impact QoL levels in PD (Den Oudsten et al., 2007).

With respect to the present study, and based on the above data; it could be hypothesised that the improvements in depression scores and mobility in the IG, may have been partly responsible for the enhanced QoL at the end of the treatment. This may be supported by the fact that all the relevant subscales (mobility, ADLs, emotional well-being) were improved significantly at post-intervention. It is unknown whether the educational sessions contributed to the positive effects of the overall QoL, or stigma and bodily discomfort subscales. The benefits on QoL in the IG are of particular interest, due to the events that occurred in Greece during the study, which could have affected the outcomes. Regarding the CG, the trivial effects of exercise on depression and anxiety, and the lack of an educational programme may have been partly responsible for the non-significant results on PDQ-39 SI scores. Interestingly, the significant effects of the home-based programme on TUG and BBS scores, did not reflect any improvement on PDQ-39 mobility and ADLs subscales.

### *Lung function*

The respiratory training favoured only the IG, as the FEV<sub>1</sub> and FVC indices were improved ( $p \leq .05$ ) from baseline to post-intervention and follow-up, and IVC from baseline to follow-up. The strength of association varied from medium to large (partial eta squared  $\geq .06$ ;  $r \geq .30$ ). On the contrary, the training failed to demonstrate any impact on Tiffeneau-Pinelli index (FEV<sub>1</sub>/FVC). Perhaps, the lack of Threshold IMT device in the home-based programme was responsible for the insignificant improvements.

Despite the fact that PD has respiratory impairments, and a restrictive, obstructive or mixed disorder, could affect half patients, usually in H&Y stages three to five (Baille et al., 2016); there is limited number of studies that have examined the effects of respiratory muscle training to improve muscle strength and lung function. Only the trial by Inzelberg et al. (2005) examined the effects of IMT using a POWERbreathe device. Although the training was effective on maximal inspiratory mouth pressure ( $PI_{max}$ ), there were no changes in the respiratory volumes and capacities. The effects of IMT have been studied more in MS, a neurological disease with pulmonary impairments as well. However, the results on lung function were mixed (Reyes et al. 2013); whereas one trial demonstrated improvements using breathing-enhanced upper extremity exercises (Mutluay et al., 2007). However, the IMT programmes in previous studies were unsupervised. Thus, the positive effects of IMT in the IG of the present study, are of particular interest, as it proved that a supervised training, with less respiratory exercise dose, could produce more improvements in lung function. However, due to the lack of a maximal inspiratory pressure (MIP) device to measure the  $PI_{max}$ , the intensity of the training was not prescribed, and progression was achieved empirically by increasing the training load of the Threshold IMT device.

Regarding the present findings, there is insufficient evidence to support the mechanism of action leading to positive effects on lung function, as the mechanism of ventilatory dysfunction in PD is poorly understood, and its aetiology may be multifactorial. IMT may lead to respiratory muscle hypertrophy increasing the mobility of the thorax, which may have been reduced, due to rigidity and bradykinesia. In turn, the increased mobility of the thorax may improve pulmonary ventilation, allowing more efficient gas exchange between the lungs and the environment (Azad et al., 2011). On the contrary, it is unknown whether respiratory training could improve all the pulmonary volumes and capacities, because the respiratory impairments in PD may also have a central aetiology. In particular, the neurodegeneration in brainstem, due to PD, could affect both the apneustic and pneumotaxic centres, which regulate respiration (Kolesnikova, 2006).

Although further investigation is needed, it seems that MDD may be linked with poor lung function, as measured by spirometry (Afreen and Ferdousi, 2016). In addition, the study by Momtaz et al. (2015) revealed that patients with COPD, who were treated with drugs for depression, improved also significantly their spirometric parameters. As the 'monoamine hypothesis' supports that physical activity may act as antidepressant medicine (Wegner et al., 2014); in the present study, it could be hypothesised that the relief of depressive symptoms within the IG, due to exercise, was partly responsible for the improvements in lung volumes and capacities. However, further evidence is needed to support this theory.

#### 10.2.4. Satisfaction level

The qualitative analysis of the SQ aimed to establish the views on therapeutic exercise intervention, in individuals with PD that participated in the current study. Patients' feedback is of particular interest in healthcare services, as it can be used to improve methods of providing health services to patients (Porter, 2008; Al-Abri and Al-Balushi, 2014). Regarding previous relevant trials on PD depression, only the effective study by Sajatovic et al. (2017) evaluated participants' satisfaction using a questionnaire with close-ended questions. The findings indicated that participants were very satisfied with the social aspects of group attendance in exercise and educational classes.

The current SQ was completed by 68.75% of patients in the IG. Only the views of those who completed the intervention period and agreed to complete the questionnaire were obtained. Perhaps, the writing difficulties due to PD, may have prevented some patients from completing the open-ended questions of the instrument. The number of completed questionnaires may have been higher if the SQ consisted only of close-ended questions. In addition, certain individuals may have disliked the structure of the programme and the interaction with other people, and found the training ineffective, avoiding to complete the questionnaire. These patients may have responded better to individualised programmes, because there is usually greater attention from their therapist. Thus, the findings of the SQ cannot be generalised, as it is unknown whether the intervention's environment was



suitable for those did not complete the questionnaire or stopped to attend the exercise class.

The collection and interpretation of data about patients' satisfaction revealed that the feedback for the exercise was positive, and most of the participants in the training commented that they did enjoy the programme. The positive feedback was accompanied with improved mood, as measured by the HADS subscales, confirming that the emotional level of patients is usually being linked with their satisfaction level (Sotgiu and Rusconi, 2013). As patient satisfaction is believed to be a multidimensional concept (Prakash, 2010); a variety of factors during the intervention period, contributed to the overall positive feedback of participants. Some of the most common reported were: the variety of exercises, the courteous attitude of instructors, and the socialising with other sufferers. Thus, the whole intervention was non-time consuming.

Not only the feedback was positive during the intervention period, but the vast majority of participants cited major beneficial aspects of the programme, apparent even from the first week of intervention. Although the majority of positive outcomes from participating in the exercise intervention were related to mobility; additional perceived benefits were related to emotional well-being, socialisation and learning through exercise. One participant also noticed improvement on lung function. The benefits the participants noticed, were in accordance with the quantitative results, which emerged that the intervention had a significant effect on mobility and mood. It is also important that the vast majority of patients did not find the programme hard to complete it. None noticed any negative effects, and minor dissatisfactions were related to the exercise venues. The proposal to add more training hours and outdoor activities in the future, revealed more the success and acceptance of the community-based programme.

An interesting finding was that despite the fact that the main goal of the current RCT was the improvement of depression, and the participants were aware of it, their priority goal to participate in the study was the improvement of motor symptoms. However, the

majority of patients with PD feel embarrassed about the non-motor symptoms of the disease or ignore that they may be related to it, reporting only the motor symptoms to healthcare professionals (Kummer and Teixeira, 2009). Lastly, the fact that some patients decided to participate due to financial difficulties to cover the physiotherapy cost, proves the need for the promotion of low-cost community-based programmes in Greece.

#### 10.2.5. Falls

To our knowledge, this is the first study to examine the characteristics of falls in patients with PD living in Greece. However, all the patients were depressed at baseline, based on the HADS-D score; and through the whole five-month reference period, they participated in a training programme to improve mood and mobility. During the whole study period overall 28 individuals (45.1%) were classified as fallers, and 19 out of 28 (67.8%) as recurrent fallers. On the contrary, the findings of the review by Allen et al. (2013), synthesising the results of 19 studies, showed that the mean proportion of fallers in PD was 60.5%, whereas 39% of them were classified as recurrent fallers. In our study, the proportion of fallers would probably be greater, if: a longer reference period was selected, and if the sample included patients with severe clinical disability level (H&Y stage four) as well; because the majority of falls usually occur at the advanced stages of the disease, when balance impairment is increased (Kim et al., 2013). Although the presence of depression could increase the number of falls and fallers, because it is believed to be a strong contributor for falls; its contribution on falls in PD has been little studied so far (Ashburn et al., 2001; Allen et al., 2013). In addition, the improvements the subjects received on mobility due to the exercise, may partly explain the less proportion of fallers. The more improvements on the primary and secondary outcomes, which were noticed in the IG compared to the CG over time, may partly explain the higher number of fallers and falls in the CG.

Logistic regression revealed that the major predictor of falls was the H&Y stage, following by the UPDRS score. The larger the H&Y stage and the UPDRS, the larger possibilities for a fall. The vast majority of fallers were in the third H&Y stage. This seems logical, as balance

impairment is a manifestation of the late stages of PD (three to five H&Y stages) (Hely et al., 2005); and the severity of gait disturbances is associated with the severity of the disease, as measured by the UPDRS (Kang et al, 2005). Surprisingly, years since PD diagnosis, age of participants, and presence of FOG were not identified strong predictors for falls, as supported in the literature (Pandya et al, 2008).

Concerning the circumstances of falling, the majority of falls happened at patient's home/property (57%), indicating that patients with PD and comorbid depression may restrict their outdoor activities even from the first stages of the disease. This proportion is lower than that reported in the study by Ashburn et al. (2008), which revealed that 80% of falls among patients with PD in the United Kingdom (UK) occurred at home. Perhaps, in the UK, due to the rainy weather, PD patients restrict further their outdoor activities. A high percentage of indoor falls in the present study, occurred at living room (23.1%), because patients may spend the majority of their day there. A significant proportion of falls (n= 39, 32.2%) occurred in the late night or early in the morning (12 am – 9 am), maybe due to the under-dosing of antiparkinsonian medication through nighttime hours. An interesting fact is that four falls occurred at late night, when the patients woke up to go to the toilet. As previously reported, at that time the medication does not work well. Only 29.7% of falls were reported during the 'on-state' of medication, when motor symptoms are well-controlled.

Regarding the activity during falling, in 68.10% of cases the individuals were ambulant, and the main reported activity that led to indoors and outdoors falls was walking (39.7%). This may arise concerns whether the patients were able to recognise their level of mobility through the day, or whether the outdoor and house environment in Greece are safe for patients with PD. Surprisingly, only 9.9% of falls occurred during turning, which is considered a high risk activity for falls; as it requires axial rotation, and is usually accompanied by FOG (Ashburn et al., 2008). However, it is believed that the actual proportion of falls during turning was higher. In particular, stairs, which accounted for 5.8% of falls, usually involve turning. In addition, almost all the respondents did not report the

direction of walking prior falling, or did not provide further information to understand the exact mechanism of falling. The relevant low percentage of standing falls (22.3%), may be explained by the fact that assistance was provided or special equipment was used for some activities with high risk of falling, such as dressing and shower.

The results also revealed that both intrinsic and extrinsic factors contributed equally to falls. However, indoors falls were caused mainly by intrinsic factors, while outdoor falls by extrinsic factors. This finding is in line with a recent study that was held in Serbia (Gazibara et al., 2014). Probably, some patients reduce or avoid outdoor activities during the off-state of medication. The main intrinsic factors were related to the motor symptoms of the disease (freezing, balance impairment); whereas dizziness accounted only for 3.3% of falls, indicating orthostatic hypotension, a major non-motor symptom of PD (Barone et al., 2009), or a side effect of medication. An interesting fact was that the reported reason of three falls was personal misjudgment of the level of foot elevation when crossing obstacles. However, it is believed that this may also be related with decreased dorsiflexion strength to cross the obstacle (Liao et al., 2014). Damaged, narrow and uphill/downhill pavements were the most reported extrinsic fall-associated factors, indicating that some neighborhoods of Athens are unfriendly for pedestrians, especially for people with disability. This may also reveal an additional factor that Greek individuals with disability, such as PD patients, may restrict their outdoor activities. Walking over a damaged pavement, curb, carpet or wet floor led to tripping. Similarly the study by Gazibara et al. (2014) reported that tripping while waking was a dominant cause of falls in Serbian PD population. The fact that no outdoor falls were cited while walking on a slippery surface, it is mainly related to weather condition in Greece during the summer period.

The reported circumstances of falls in the IG, raised issues whether the educational programme managed to educate patients how to overcome gait difficulties and avoid falling. However, it is supported that despite the fact that some patients with PD may be aware of the factors leading to falls, they feel confident while performing activities with high risk of falling (Rahman et al, 2008). Alternatively, some patients may recognise their

current mobility limitations, but continue to perform their ADLs independently, as they wish to preserve their autonomy.

Based on participants' answers, 26.5% of the reported falls were injurious. Nearly  $\frac{3}{4}$  of the injuries occurred outdoors, and caused mainly by extrinsic factors. The most commonly injuries were minor, and specific medical intervention was not required. Only two lacerations required sutures, and there were no fractures. The increased BMI of participants may have decreased the risk of bone fractures (Bachmann and Trenkwalder, 2006). These results are similar to those one that found in Serbia, where the majority of injurious falls occurred outdoors (Gazibara et al., 2014); and in contrast with the findings that reported in the UK, where 65% of injurious falls happened at home (Ashburn et al., 2008). It seems that in the UK, apart from the fact that PD patients may restrict their outdoor activities due to the weather conditions, there may be less extrinsic factors leading to outdoor falls compared to Balkan countries (e.g. less damaged pavements, more flat pavements, less outdoor stairs).

#### 10.2.6. Drop-out reasons and attendance rate

In the present study, the overall drop-out rate, from the baseline up to the follow-up, was 13.3%. It seems that the strict eligibility criteria, in combination with the screening procedure, assisted to select participants suitable for the nature of the study; and individuals with comorbidities, which may affect their participation to the programme, were excluded. Secondly, the selected venues were easily accessible by public means of transportation or personal automobiles. The individuals who expressed interest to participate in the study, were placed in municipalities closed to their place of residence to ensure fast access to the selected venues. The community-based and home-based programmes were not monotonous, including a variety of exercises to keep the interest of trainees. It is also believed that the free-of-charge-participation was an additional important factor to complete the programme, as due to the ongoing debt crisis some patients were unable to cover their healthcare expenditures.

Concerning the CG, the high attendance was also achieved by: telephone calls to ensure their participation to the training (Ravenek and Schneider, 2009), and the offer of the group exercise and educational programme, if the results would have been significant (Berger et al., 2009). However, the lower drop-out rate in the IG could be explained by the: systematic selection of the exercise dose to achieve high attendance (section 8.8.1), the interactive nature of the educational lectures, the highly exercise supervision by professionals with expertise in PD, the motivation provided by the healthcare providers, the facility-based environment (Allen et al., 2012; Stubbs et al., 2016), and the socialisation aspects of the group attendance.

The most important finding was that the exercise intervention did not cause a detrimental effect on patients; providing further evidence to the current knowledge of the present systematic review (Section 4.6.2), that therapeutic exercise is safe in this population, if the programme is organised by experienced healthcare professionals, and a careful assessment ensures the ability for participation. It is of particular interest that none of the individuals left the programme or made absences due to an injury during training, or because the programme was exhausting or boring. More interestingly, a further investigation of individuals who left the IG and CG from baseline to post-intervention, revealed that the mean HADS-D score was 10.8 and 12.4 for the IG and CG respectively at baseline, indicating that more severe levels of depression in unsupervised programmes may likely result in a higher drop-out rate. However, further research is needed to confirm this finding.

### **10.3. Methodological issues- strengths and limitations**

#### **10.3.1. Strengths of the current study**

The strengths of the present study should be recognised. The RCT was unique in a number of areas. It was the first to: establish the impact of a therapeutic exercise programme combined with education on depression to those affected with PD, include only individuals with elevated levels of depression, use a self-report tool to detect participants' satisfaction about the exercise programme. With reference to Greece, it was the first study to assess

the effectiveness of a community delivered exercise and educational programme and report the number and characteristics of falls in Greek population living with PD.

The CONSORT guidelines were followed to increase the quality of the study; ensuring less possibilities for bias; and achieving adequate internal and external validity (Moher et al., 2010). The strict eligibility criteria ensured that the participants met the standards to participate in the study, they were not vulnerable to harm from the study intervention, and that any improvement was a result of the intervention. (Elkin and Moseley, 2015). The inclusion criteria also enabled to have an homogeneity of participants, which allowed researchers to generalise the results and conclusions to the population being studied (Leonard et al., 2003). The randomisation procedure guaranteed that none of the study groups had an advantage over the other. Trials with inadequate or unclear randomisation tend to overestimate treatment effects up to 40% compared with those that use proper randomisation (Schul and Grimes, 2009). The rigorous eligibility criteria, the randomisation procedure and the concealed allocation reduced the possibilities for selection bias, and any difference between the study groups at baseline reflected chance (Pannucci and Wilkins, 2010).

A sample size calculation was performed to determine the number of participants needed to detect a clinically relevant treatment effect. Thus, based on the sample size determination, the study had sufficient power to detect a worthwhile change. In order to avoid attrition bias, due to the loss of the participants through the whole study period, more participants were enrolled than the minimum required sample size. However, although this step is important, it is not sufficient to totally avoid bias, even if the number of remaining patients is enough to give the required statistical power (Nunan et al. 2018).

The design of the intervention was appropriate for the target population, the landscape of Greece and the purpose of the study. Due to the scarcity of indoors equipped exercise venues in the Greek municipalities; it was decided to design a low-cost programme, without expensive and sophisticated equipment, which could be performed even in the small cities

of the country, under the supervision of experienced healthcare providers. The training protocol combined evidence-based elements of exercise in PD and depressed population. In addition, some lectures of the educational programme were designed based on the findings of the present survey, to cover the needs of Greek patients with PD. The treatment setting was the same for all the groups of the IG; hence, there was not an advantage of one group against another (Dekkers et al., 2010). The pilot work enabled to test the preliminary design, before the conduction of the main study (Thabane et al., 2010). The interventions were described thoroughly, allowing the clinicians to know exactly how to administer the interventions that were evaluated in the trial (Moher et al., 2010). Lastly, in an era that there is increasing interest for long-lasting effects in healthcare, the current RCT assessed both the shorter- and longer-term effects of the intervention.

Special emphasis was given to the screening and assessment procedure to avoid patients' fatigue, any flaws during the whole procedure, and to reduce assessment time. There was an attempt to use tools with high clinimetric properties to reduce measurement error, which have translated and validated in the Greek language. The HADS-D was the selected measurement tool for depression, the primary outcome of the study; because it is valid tool in PD to monitor changes in depression, irrespectively the progress and the severity of motor symptoms. A strict procedure was followed for the construction of FQ and SQ, as described in the surve, to eliminate possible type of bias and receive accurate responses (Choi and Pak, 2005). The printed versions of self-administered instruments were friendly for the current population to facilitate their completion. The absence of an interviewer for the completion of FQ and SQ provided greater freedom to the respondent; and there was no interviewer bias, caused by the variability in interviewers' skills (Choi and Pak, 2005). The screening procedure and assessments were performed by trained staff, and a specialist neurologist ensured that only patients with PD were included in the study. In addition, the more sensitive tools for the confirmation of PD and detection of depression were conducted first. Thus, individuals that were ineligible for participation became apparent early in the process. With respect to the assessments, all the clinical tests were performed by the same assessor (chief investigator), who had previous experience in using these tools, following specific protocols. Moreover, the pre- post- and follow-up assessments were



performed about the same time of the day to minimise within-day variability. Lastly, it is believed that due to the systematic design of the whole study, detrimental effects were not seen.

Regarding the data analysis, a mixed methodological approach by collecting and interpreting both objective and subjective data, was selected to strength the effectiveness of the intervention. Although the p value indicates whether an effect exists, it does not reveal the size of the effect (Sullivan and Feinn, 2012). Therefore, both the substantive (effect size), statistical (p value) and clinical significance (MCID) were reported in the results. In addition, the responses of participants in the SQ established the views on group-based therapeutic exercise intervention, highlighting its benefits. The study also reported both the statistically significant and non-significant results minimising the danger of selective reporting bias (Pannucci and Wilkins, 2010).

Despite the aforementioned strengths, it seems that the most positive outcomes of the community-based programme were that: it enhanced the socialisation of participants, provided them the feeling of being a member in a community, and motivated them to increase their outdoor activities. As both the participants' feedback was positive, and the objective data showed that the study was effective; the HPDA 'Epikouros-kinisi' decided to offer the group-based programme free-of-charge to its members living in Athens in co-operation with volunteer physiotherapists. This was the first time the HPDA has offered a treatment to its members, as until that time its main aim was the information of patients and their families about the treatment options of the disease and healthcare advice. The first exercise classes started in December 2015 in four municipalities, and three more municipalities were added the following year. The programme was enhanced with: speech therapy sessions, education and psychological support of carers and families of people living with PD, and lectures in public venues to inform Greek population about PD. In an attempt to establish active PD communities in the municipalities of Athens, and promote socialisation between its members, the HPDA arranged meetings in each municipality on a monthly basis and half-day trips once a month. Bazaars and sponsorships helped the

organisation to collect money for this purpose. There were also plans to incorporate and alternatives types of physical activity, such as traditional Greek dances and Tai Chi training. Unfortunately, due to the small number of volunteers and for logistical reasons, the programmes stopped in June 2017. However, there are plans to start again in the near future.

### 10.3.2. Limitations of the current study

Certain limitations of the study should be acknowledged. Firstly, it is important to cite the main drawbacks on the generalisability of the current findings. Despite the fact that the participants were outpatients and strict eligibility criteria were defined; it seems that in studies in PD, which examine the effectiveness of an approach; younger PD patients, females, with higher educational level are more likely to participate. Thus, there is a danger for volunteer bias (Moore et al., 2014). In addition, in the present RCT, the participants had to be members of the HPDA. Perhaps, some potential participants may have refused to participate in the study, as they were reluctant to enroll with the HPDA.

Secondly, the determination of depression was adapted by the self-rated HADS-D, and a clinical diagnostic assessment using the gold standards (semi-structured interview DSM or ICD criteria) was not performed. Thus, it is possible that some participants did not meet diagnosis for clinical levels of MDD. When a cut-off of 11 was selected to distinguish depressed from non-depressed population; only 24 out of 62 participants exceeded the minimum score for clinical depression. However, the results at post-intervention and follow-up indicated that the community-based exercise and educational programme reduced significantly the depressive symptoms.

Although there was an effort to select assessment tools with high clinimetric properties, this was not always possible; due to the unavailability of equipment, non-translation and validation of some instruments in the Greek language. Thus, measurement tools with higher clinimetric properties, which are recommended to the target population were

rejected. Moreover, in contrast with previous studies in PD, neither the total UPDRS nor the UPDRS-III (motor subscale) scores were used to assess the effectiveness of the intervention at the end of the treatment. Although the self-administered tools, which were selected, appear high clinimetric properties and are proposed in PD (HADS, PDQ-39, FES-I); the accuracy of responses was solely based on participants' views. As the participants were not blinded to the allocation, the members of the IG may have overestimated the treatment effects, increasing the possibilities for measurement bias. There is also danger for recall bias, because the subjects may have not remembered previous events, behaviours and experiences accurately (Pannucci and Wilkins, 2010).

The self-administered questionnaires (FQ, SQ), designed by the chief investigator, were not free of limitations. The SQ did not include any question about the educational sessions. Hence, the individuals' satisfaction relevant to the educational component, was not recorded. Furthermore, the open-ended questions of both questionnaires may have been inappropriate for the target population, due to writing difficulties even from the first stages of the disease. This may partly explain the low response rate in the SQ, and the inaccurate responses about the mechanism of falls (question four) in the FQ.

In addition, the study did not aim to explore the mechanisms that may have been responsible for the improvements in depression and the secondary outcomes. The participants did not complete any physical or physiological test or self-report questionnaire for this purpose. Hence, it is unclear whether some mechanisms, which are proposed in the literature, contributed to the study's outcomes.

Despite the fact that an attempt was made to minimise potential bias, this was not always possible. As both subjects and therapists were unblinded to subjects' allocation, the study was prone to performance bias. However, in studies where exercise is the intervention, the masking of participants and therapists is not possible. Furthermore, as the assessors were also unblinded, there was risk for detection bias, which could overestimate or underestimate the intervention's effect (Pannucci and Wilkins, 2010). Lastly, an intention-

to-treat analysis, based on the worst or best case scenario, to identify the real effect of the intervention (Elkin and Moseley, 2015), was not performed, as it was not in the initial plan of the study.

#### **10.4. Recommendations for future research**

A small number of studies rarely provides enough evidence to guide clinical and research practice. Furthermore, there is need for effective community-based programmes, due to their lower cost compared to individual supervised training. Thus, future studies should explore further the impact of exercise interventions on depression in patients with PD. However, it is difficult to make a prior estimation on the effectiveness of the present intervention in different countries. As different cultures may influence mood (Dekkers et al., 2010), it would be useful to conduct the current intervention protocol in other countries to conclude whether would reveal any antidepressant effect.

It is recommended for future studies to focus on depressed population with PD, using accurate diagnostic tools for the clinical diagnosis of depression. The most commonly tool is the Structured Clinical Interview for DSM, through which diagnosis is made by psychologists according to DSM criteria (Gazzaniga et al., 2010). Thus, it will be investigated whether the present intervention could produce significant antidepressant effects in a clinically depressed population with PD. Longer periods of follow-up will provide further information about the longer-term effects of the intervention.

It is also recommended to select tools with higher clinimetric properties for the screening procedure and assessments, which were not translated and validated in the Greek language at the time this study was conducted. This is feasible in trials with English-speaking population, as all the tools are available in the English language. To illustrate the point, the clinician-rated scales HAM-D and MADRS could be selected to monitor changes on depression; the MoCA test to assess cognitive function; FOG Questionnaire for the severity and frequency of FOG episodes; Mini-BESTest for functional balance; and M-PAS

for functional mobility. Lastly, a design of a FQ and SQ consisting mainly of close-ended questions, may be more suitable for this population, due to the writing difficulties.

Moreover trials of higher methodological quality than the present study, will produce less bias, increase the internal and external validity, and allow to strong firm conclusions about the effectiveness of exercise in PD population suffering from depression. Hence, based on the limitations of the present study, it is recommended to use blinded assessors; and to conduct an intention-to-treat analysis in order to estimate the real effect of the intervention.

In addition, the mechanisms of action should be explored further, in order to provide an in-depth understanding about the mechanisms that contribute and interact to each other to improve depression and anxiety in PD. Thus, the participants could complete physical or physiological tests to investigate the presence of biological mechanisms, such as: the enzyme-linked immunosorbent assay (ELISA) test for markers of neuroprotection, endorphins, and inflammatory cytokines (e.g. BDNF, VEGF,  $\beta$ -endorphins, IL-6) in blood; the dexamethasone suppression test (DST) to assess adrenal gland function by measuring the cortisol levels; the urinary neurotransmitter testing (UNT), which may indicate imbalances between the neurotransmitters; MRI for the measurement of brain volumes (i.e. amygdala, thalamus, hippocampus), which are associated with anxiety and depression. Similarly, self-report questionnaires could explore the role of socio-psychological theories. Indeed, SEE scale and questionnaire could provide evidence about the 'self-efficacy theory'. Self-report questionnaires designed by the researchers, could reveal information about the role of the 'distraction hypothesis' and 'social interaction hypothesis' in reducing depression in PD, due to exercise and education.

As improvements in depression may be correlated with improvements in sleep, due to exercise; (Singh et al., 1997); future studies in depressed patients with PD should examine if any beneficial effect of training on depression is related with better quality of sleep or more sleeping hours. For this purpose, the SCOPA-S and Parkinson's disease Sleep Scale

could be used to assess the quality of sleep before and after treatment (Chaudhuri et al., 2002). The mechanism of action could also be explored for the secondary outcomes of the study. Indeed, the muscle strength test, cardiorespiratory test and gait analysis, will provide information about the results of the intervention on mobility; whereas a MIP device about lung function.

Modifications of the present exercise protocol, based on the available equipment and exercise dose; could produce further antidepressant effects, improvements on mobility and lung function. Current evidence supports the use of CMS to facilitate learning and movement, and increase the muscle strength; exercise on the floor could improve trunk mobility; indoors aerobic exercise in a prescribed intensity using equipment (e.g. treadmill and stationary bicycle) could improve cardiorespiratory fitness and alleviate symptoms of depression; and expiratory muscle training (EMT) could improve the obstructive respiratory pattern of patients with PD. Suggested methods of prescribing relative exercise intensity are: the measurement of HRR for aerobic training; and  $PI_{max}$  and maximal expiratory mouth pressure for respiratory muscle training (Mann et al., 2013). As some participants cited that they did enjoy the ball exercises, future studies could incorporate to their programme more activities that promote interaction among the trainees of the exercise group. Alternative, unstructured physical activity –such as Tai Chi, Yoga, box and dance- may provide more enjoyment and be more effective to improve mood than structured exercise. Regarding, the unsupervised home-based training; a CD or a smartphone/tablet application including videos with exercises, could facilitate patients to perform the training by themselves. This may be important for some regional and rural patients with PD, who lack access to healthcare facilities.

An additional control arm receiving usual care will allow direct comparison of intervention with no intervention. Similarly, the split of IG in two groups, one receiving group exercise and another educational classes, will reveal the degree at which each component contributes to antidepressant effects. At a time that there are many recommended treatment options for depression, and as some studies in depressed population revealed

that exercise is comparable or more effective than psychological approaches to improve mood (Schuch et al., 2016b); it would be of particular interest for future studies in PD, to compare exercise with psychological approaches (e.g. CBT), or combine both treatments, in order to find the treatment that produces the best results. As the direct and indirect cost of PD is high, a final avenue that should be explored is the financial cost of all the effective treatment options for depression in PD, in order to promote the less cost effective option.

The present RCT revealed also some additional gaps in the research and in the healthcare services in Greece, which should be addressed. As the MCID is important in clinical practice to assess the progress of a treatment; future research is recommended to establish the MCIDs values for the HADS-A, HADS-D, BBS, FES-I, TUG and 2MWD in PD population. Further research should also determine the optimum cut-off score to distinguish depressed and non-depressed population in PD using the HADS-D. In addition, the knowledge of Greek healthcare professionals working with those with PD should be investigated. Their continuing professional development will assist them to provide their clients with the most effective treatment. Lastly, as some patients reported low social support or abuse by their family, and given the fact that family is the main caregiver of patients with chronic diseases in Greece; the education of family will reduce caregiver's burden, improve the provided services for patients at home, and in turn will probably improve patients' emotional well-being and QoL.

### **10.5. Conclusion**

In conclusion, the current RCT revealed that only the community-based intervention managed to alleviate depressive symptoms; however, there was not any significant difference between the two groups at post-intervention and follow-up. Not only the p value and the effect size revealed that the group exercise and educational classes produced antidepressant effects; but the participants of the IG did cite that the training assisted them in a significant extent on mobility and emotional well-being, enhancing the findings of the statistical tests. Within the PD therapeutic exercise literature, similar significant improvements in depression have also been reported. However, the current study was the

first that included PD population with elevated levels of depression, and a sample size determination confirmed that the trial had sufficient power to detect a worthwhile change. As the results of a single RCT cannot draw strong conclusions about the effectiveness of community-based therapeutic exercise and education in PD population with elevated levels of depression, there is scope for continued clinically relevant research for those with PD, with an improvement in study quality. Despite the significant results and the provision of useful information in clinical setting, the most positive outcome of the present RCT was the establishment of PD communities in seven municipalities of Athens Metropolitan Area, and the free-of-charge multidisciplinary approach that was offered to PD patients and their carers by experienced healthcare professionals under the auspices of the HPDA 'Epikouros-kinisi'.

#### **10.6. Summary of Chapter 10**

- The study groups were similar at baseline regarding the basic socio-demographic characteristics, health status, and outcome measures; probably due to proper randomisation procedure and concealed allocation.
- The small or medium relationship of anxiety and depression with anthropometric characteristics, health status and secondary outcome measures may have resulted due to the complex concepts of mental disorders in PD.
- The lack of physiological and physical tests did not allow the establishment of the biological and psychological mechanisms that improved mood. Thus, only assumptions were made.
- The motivation provided by the healthcare providers, the social interaction between the participants, the dose and type of exercise, the improvements in mobility, and the content of educational classes; may have been the determinants for the significant antidepressant effects in the IG.
- The current findings were in line with previous research in PD; where therapeutic exercise programmes, educational classes and multidisciplinary approaches managed to alleviate depressive symptoms. However, the present RCT was the first that included only PD patients with elevated levels of depression. Before the submission of the



current thesis, a study (Sajatovic et al., 2017) with similar design, which included only PD patients diagnosed with MDD, was published.

- Caution is needed for the interpretation of secondary outcomes as the study's design was based on the key outcome, and any change may reflect chance.
- It seems that the effects of exercise on neuroprotection and neuroplasticity may have been responsible for the improvements in mobility in both study groups.
- The trivial improvements in FES-I scores may be explained by the fact that FOF in PD is complex, and is affected by many factors.
- The improvements in anxiety, depression and mobility may partly explain the beneficial effects of the community-based exercise and education on QoL.
- Despite the fact that the pathophysiology of respiratory impairments in PD is not well-established, the IG showed some improvements in lung function, as measured by the spirometre. However, it is unknown whether the antidepressant effects of training were partly responsible for these benefits.
- The most valuable outcome of the present study was the establishment of PD communities in seven municipalities of Athens and the free-of-charge treatments provided to patients with PD and their carers by the HPDA.
- The present RCT also confirmed that exercise is safe in PD population, when strict eligibility criteria are used for the selection of participants, and the whole programme is supervised by healthcare providers with expertise in PD.
- Additional studies are proposed using rigorous methodology, to draw strong conclusions about the effectiveness of therapeutic exercise and education in PD patients with clinical levels of depression. The mechanism of action of exercise and education on mood in people with PD should be explored.
- The analysis of FQ revealed that the majority of falls were recorded at the patients' home, maybe due to the restriction of outdoor activities; however, the largest proportion of fall-related injuries occurred outdoors, caused mainly by extrinsic factors.

# **CHAPTER 11**

## **OVERALL CONCLUSION**

### **11.1. Introduction**

Depression is one of the most common non-motor symptoms in PD population. It is associated with worse physical functioning, increased fall rates, reduced QoL, further direct and indirect cost, and it is an important predictor of mortality in PD. Despite its high frequency and significant burden in PD, depression is seldom diagnosed and often untreated. Although therapeutic exercise seems to be an important adjunct to the available pharmacological and psychological treatment for the management of depression in the overall population, the role of exercise to relieve depressive symptoms in those affected by PD, has received less attention.

Thus, the overall aim of the present thesis was to address gaps within the research, relating to the role of the therapeutic exercise to alleviate depressive symptoms in patients with PD and co-morbid depression. In particular, the systematic review aimed to summarise and evaluate the evidence deriving from all the available RCTs, which examined the effectiveness of therapeutic exercise on depression in PD population. Further, a survey was performed to detect and list the impacts of PD on ADLs and emotional status in patients with PD living in Greece; whilst the most prevalent responses were considered for the design of the RCT's intervention. Lastly, an RCT was conducted to examine the effectiveness of a community-based exercise and educational programme on depression in Greek population living with PD.

### **11.2. Innovative studies and contribution to knowledge**

All three studies were innovative in a number of ways and added unique knowledge to the literature.

The current systematic review was the first that provided an insight into the connection of physical activity with depression and anxiety in PD. The review revealed that depression and anxiety in PD were rarely examined as primary endpoint; and the presence of depressive and anxiety disorders was not among the eligibility criteria of the studies, as

detected by accurate diagnostic criteria or rating scales. As the findings of previous RCTs were controversial, there was insufficient evidence to determine whether exercise was able to elicit short- and longer-term antidepressant and anxiolytic effects. Hence, future studies were recommended to fill this gap. In addition, the review did not manage to inform clinicians about the optimal type and dose of exercise to manage depression and anxiety in PD, due to the diversity of the interventions among the effective trials. On the contrary, it was proved that exercise is a safe, non-harmful approach for this population.

Regarding the survey, no previous work was found to record the level of mobility and emotional status in Greek population living with PD. A disease-specific questionnaire, with both close- and open-ended items, was designed for this purpose. The fact that the respondent could be either a patient with PD or carer, may have assisted to include in the survey's sample patients, who may have being unable to complete the questionnaire for a variety of reasons, such as writing difficulties and advanced levels of disability. The items of the questionnaire relevant to the socio-demographic features and health status, were in accordance to Greece's landscape. The open-ended question, at the end of the instrument, allowed respondents to record personal beliefs about their experience living with PD. The results demonstrated that PD does not only affect physical function, even from the first stages of the disease, reducing the social life of patients; but it also affects mental health and provokes negative thoughts, both for the patients and their carers. Despite the survey's small sample, the results indicated that due to restrictions in mobility and emotional well-being, there is need for improved care and better overall treatment options for those with PD living in Greece.

Lastly, the RCT was unique in a number of areas, and as such adds substantial knowledge to the literature surrounding therapeutic exercise in PD. It was the first to: establish the impact of a therapeutic exercise and educational programme on depression in patients with PD; and include only of individuals with elevated levels of depression, as measured by the HADS-D. As the RCT was held in Athens; this was the first study that promoted community-based exercise in Greece, and recorded the number and features of falls in

Greek PD population. The strict eligibility criteria enabled to have an homogeneity of participants and reduce the external factors that may have affected the results.

In order to meet the study's aim; a group-based exercise and educational programme, and a booklet for individualised home-based exercise were designed by the author. As the results of the current survey were consulted for the whole design of the intervention, it is believed that the major needs of patients with PD living in Greece were covered. In an era that there is an increasing interest about the treatment cost, inexpensive and sophisticated equipment was used for the exercise classes. Simple exercises and measurement tools were selected, which did not require special training of therapists and are completed in a short time. As the whole protocol is described thoroughly, the programme can be reproduced even from physiotherapists not specialised in PD.

In addition, due to the sample size determination, the RCT had sufficient power to detect a worthwhile change. Apart from the statistical (p value); the substantive (effect size) and clinical (MCID value) were reported in the results. The MCID value is necessary to clinicians in order to check the response to the treatment. In addition, the participants' satisfaction on the group-based exercise programme was recorded, adding much to the qualitative research in therapeutic exercise in PD.

The results of the RCT demonstrated that depressed patients with PD are able to obtain short- and longer-term antidepressant benefits from commencing a well-designed, structured exercise and educational programme, provided by allied healthcare professionals with expertise in PD. The fact that the intervention was able to elicit antidepressant effects is extremely important, since this was the first study to recruit only PD patients with elevated levels of depression. The intervention managed to relieve depression, in spite of the events that occurred that period in Greece, and could have had a negative impact on the outcome. Despite the fact that the subjects did not perform any test, in order to detect the biological and psychological mechanisms that improved depressive scores; assumptions were made based on the literature. Not only the benefits

were produced in a relevant short time frame; but the intervention had also positive effects on mobility, QoL and lung function. The positive results in the primary and secondary outcomes were also confirmed by the participants, enhancing the effectiveness of the treatment. Moreover, an important finding of this study was that no adverse effects due to exercise were noted. However, it seems that the most positive outcome was the establishment of PD communities in seven municipalities of Athens Metropolitan Area, where the group-based exercise programme was offered free-of-charge by the HPDA 'Epikouros-kinisi' and its volunteers.

Until the submission of the current surveys a similar systematic review (Wu et al., 2017) and a RCT (Sajatovic et al., 2017) were published. However, the present work was superior for a number of reasons. The review by Wu et al. (2017) included both experimental and quasi-experimental studies, which increase the possibilities for selection bias; and trials, where exercise was combined with an additional treatment, making it difficult to know the extent to which exercise influenced depression. In addition, the literature search was limited from 2006 to 2017. The RCT by Sajatovic et al. (2017) presented the findings only for the combined group, not allowing conclusions to be drawn for the group-based exercise and education intervention; and limited information was provided for participants' satisfaction.

### **11.3. Recommendations**

Clinical and research recommendations emerged from this thesis. The current Section summarises the proposals for implementations and future research, which have already been reported in Sections 4.7.7, 7.5 and 10.4.

#### **11.3.1. Recommendations for rehabilitation practice**

Community-based programmes combining exercise and educational classes seem to be an effective adjunct treatment to relieve depressive symptoms and improve mobility and QoL in PD population with elevated levels of depression. Hence, group-based exercise and

education could be used as an alternative, affordable therapeutic option for depression in PD. Along with the benefits on emotional well-being, therapeutic exercise is the only treatment that could improve mobility and cardiorespiratory fitness. The programme could be feasible even in small cities of Greece and in different countries, as expensive and sophisticated equipment is not required; just healthcare providers with some expertise in PD. In addition, the supervision of exercise by expert staff negates the risk of adverse effects. As the design of exercise was based on combined data in depression and PD, in order to improve both the primary and secondary outcome measures; it is believed that the programme is suitable even for those with mild to moderate PD (H&Y stages one to three) without elevated levels of depression.

Furthermore, the healthcare professionals in order to develop and propose new strategies for the management of the disease, they should recognise and understand the needs of PD patients, and the aspects of the disease that may have a determinant impact on their daily lives. Thus, it is believed that an instrument similar to what was designed for the survey, could be a valuable tool to assess the extent to which each activity or emotional symptom may affect the daily life of patients; and should be included as a standard procedure for monitoring and evaluation of both individual and group rehabilitation programmes.

### 11.3.2. Recommendations for future research

The positive results of a limited number of experimental studies are not enough to draw strong conclusions for the benefits of a treatment. Accordingly, further work is required to ascertain the potential effect of exercise, combined or not with education, on depression in PD; and provide guidance to clinical practitioners. It is recommended to future trials to focus on clinically depressed population, as defined by the DSM or ICD criteria; and select screening and assessment tools, which are highly recommended on this population. As different cultures may influence mood, it would be useful to conduct the current intervention protocol to other countries to conclude whether it is effective or not. Modifications of the current protocol for both the group-based and individualised programme, may produce more antidepressant effects. As the p-value is not considered

enough to conclude the success of an approach; the effect size, confidence interval, the MCID value, the participants' satisfaction and the intervention's safety should be recorded.

In addition future studies of high methodological quality should detect the exercise type and its dose to relieve depression in PD population. Thus, they should focus on several types and doses of exercise, compare and/or combine exercise with other treatments; in order to assist healthcare professionals to offer the best treatment option to patients, based on their needs and preferences. Moreover, the evaluation of the financial cost of all the effective treatment options for depression in PD, will assist the NHS and private companies in the health sector to promote the most cost effective option. The biological and psychological mechanisms, responsible for the relief of depressive symptoms in PD, population should also be explored; whereas the establishment of the MCID values for rating scales that assess depression in PD population, will assist clinical practitioners to evaluate the effects of the treatment.

Regarding the limitations of the present survey, there is need for larger nationwide studies in Greece to ensure the geographical coverage of the whole country, and for a study that will reach social groups, which are hard to participate in surveys (e.g. ethnic minorities, immigrants). It is believed that a shorter questionnaire may increase the response rate. Similar international studies could detect the socio-demographic characteristics, health status, level of mobility and emotional well-being of patients with PD. However, patients with PD should be consulted for the construction of the instruments, and the steps proposed by the WHO should be followed for the translation and adaption of the questionnaire in different languages. The recording of restrictions in the daily life of patients with PD, will contribute to a deeper understanding of their needs, and will assist the NHS of each country to set new goals for the management of PD, and promote the most effective treatment options for this purpose.



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## APPENDICES

**Appendix 3.1.**Types and diagnostic criteria of depressive disorders.*Major depressive disorder*

MDD -also called ‘major depression’ or ‘clinical depression’- is defined by one or more major depressive episodes (MDE) and the lifetime absence of mania and hypomania. It is characterised by severe negative moods; such as sad, hopeless, lack of interest in normally pleasurable activities. To meet the criteria for a MDE, it is required that five of nine symptoms, as seen in table A.1, are present during the same two-week period (Uher et al., 2014).

Table A.1. DSM-V criteria for major depressive disorder (adopted from Uher et al., 2014).

A Five or more out of nine symptoms (including at least one of depressed mood and loss of interest or pleasure) in the same 2-week period. Each of these symptoms represents a change from previous functioning.	
Note: symptoms that are clearly attributable to another medical condition are not included.	
Symptoms	Frequency requirements
1. Depressed mood (subjective or observed)	Most of the day, nearly every day
2. Loss of interest or pleasure	Most of the day, nearly every day
3. Change in weight or appetite	Appetite: Nearly every day Weight: 5% change over one month
4. Insomnia or hypersomnia	Nearly every day
5. Psychomotor retardation or agitation (observed)	Nearly every day
6. Loss of energy or fatigue	Nearly every day
7. Feelings of worthlessness or guilt	Nearly every day
8. Impaired concentration or indecisiveness	Nearly every day
9. Thoughts of death or suicidal ideation or attempt	Thoughts: recurrent Attempt: any
B. The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.	
C. The episode is not attributable to the physiological effects of a substance or to another medical condition.	
D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.	
E. There has never been a manic or hypomanic episode	

Between MDEs, more sufferers are asymptomatic, but about 30% experience some residual symptoms; which are grouped in four categories: sleep disturbances, affective, somatic and cognitive symptoms. The most frequent affective symptoms are: depressed

mood, loss of interest and pleasure, and low interest in work; whereas the most frequent somatic symptoms include: fatigue, gastrointestinal symptoms, back pain, muscle ache, joint pain and sexual dysfunctions (Uher et al., 2014).

The DSM-IV-TR recognises five subtypes of MDD, which are listed as follows:

- Atypical depression, which is characterised by improved moods in response to positive events (Benazzi, 2006).
- Catatonic depression is diagnosed when someone who is suffering from MDD develops physical symptoms; such as being unable to move, speak or respond to external stimuli (Benazzi, 2006).
- Melancholic depression, which is characterised at least by anhedonia or lack of mood reactivity (Benazzi, 2006).
- Postpartum depression, which affects mainly female population after childbirth (Benazzi, 2006).
- Seasonal affective disorder is a cyclical pattern of depression, in which individuals exhibit depressive symptoms at the same period of each year, more commonly during winter months. It is usually reported in northern latitudes during the shorter days of winter (Benazzi, 2006).

### *Dysthymic disorder*

Dysthymic disorder is also called ‘mild depression’ or ‘chronic depression’. It is a low-grade, persistent depression (Benazzi, 2006). Periods of dysthymia last for two to twenty years, although the typical duration is about five to ten years (Paykel, 2008). Dysthymic disorder sufferers typically experience milder depressive symptoms than MDD (Benazzi, 2006). However, in DSM-V, the new category of persistent depressive disorder (PDD) aims to combine dysthymia and chronic depression. Thus, except DSM-IV diagnosis for dysthymia, individuals whose symptoms meet MDD criteria for two years are given a diagnosis of PDD. In addition, the sufferers should not be without symptoms for more than two months (Uher et al., 2014). The criteria of PDD, according to DSM-V, are presented in table A.2.

Table A.2. DSM-V criteria for persistent depressive disorder (adopted from Paykel, 2008).

A. Depressed mood for most of the day, for more days than not, as indicated by either subjective account or observation by others, for at least 2 years.
B. Presence, while depressed, at least two of the following: 1. Poor appetite or overeating. 2. Insomnia or hypersomnia. 3. Low energy or fatigue. 4. Low self-esteem. 5. Poor concentration or difficulty making decisions. 6. Feelings of hopelessness.
C. During the two-year period of the disturbance, the individual has never been without the symptoms in Criteria A and B for more than two months at a time.
D. Criteria for a major depressive disorder may be continuously present for two years.
E. There has never been a manic or hypomanic episode, and criteria have never been met for cyclothymic disorder.
F. The disturbance is not better explained by a persistent schizoaffective disorder, schizophrenia, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.
G. The symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hypothyroidism).
H. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

# Appendix 4.1. Data extraction tool.

Publication data	
First name author	
Year of publication	
Country	
Participants	
Sample size	
Gender proportion	
Disease severity	
Mean age	
Mean duration of PD	
Intervention	
Type of exercise	
Setting	
Exercise format	
Supervision	
Description of exercise protocol	
Programme duration	
Exercise frequency	
Session length	
Exercise intensity	
Comparison	
Type of comparison	
Description of protocol	
Outcomes	
Outcome measure	
Primary/secondary outcome	
Assessment tool	
Mid-term results	
Post-intervention results	
Follow-up results	



**Appendix 4.2.** Brief description of the PEDro scale.

The PEDro scale contains 11 items. For each item, a 'yes' or 'no' response is obtained. A 'yes' response earns one point, whereas a 'no' response receives zero points. Points are only awarded when a criterion is clearly satisfied and reported. Item one is excluded from the total score, as it is related to the external validity of the study. Criteria two to nine examine the study's internal validity, and criteria ten and 11 are related to the interpretation of results. Thus, the total PEDro scale score ranges from zero to ten, with a higher score indicating better methodological quality (Sherrington et al., 2000).

**Appendix 4.3.** Quality appraisal tool. The guidelines how to complete the PEDro scale are reported in the link: <https://www.pedro.org.au/english/downloads/pedro-scale/>

### PEDro Scale

**First author name:**

**Year of publication:**

**Title of article:**

Criterion number	PEDro criteria	YES	NO
01	Eligibility criteria were specified		
02	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)		
03	Allocation was concealed		
04	The groups were similar at baseline regarding the most important prognostic indicators		
05	There was blinding of all subjects		
06	There was blinding of all therapists who administered the therapy		
07	There was blinding of all assessors who measured at least one key outcome		
08	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups		
09	All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"		
10	The results of between-group statistical comparisons are reported for at least one key outcome		
11	The study provides both point measures and measures of variability for at least one key outcome		

**Total score:**

/10

**Overall quality:**

Excellent (9-10)	
Good (6-8)	
Fair (4-5)	
Poor (0-3)	

**Appendix 4.4.** Excluded full-text articles and reasons of exclusion.

Number of studies (All 27)	First author name and year of publication	Reason of exclusion
7	<ul style="list-style-type: none"> <li>• Blandy (2015)</li> <li>• Boulgarides (2014)</li> <li>• Cheon (2013)</li> <li>• Cruise (2011)</li> <li>• Dereli (2010)</li> <li>• Pellecchia (2004)</li> <li>• Tanaka (2009)</li> </ul>	Lack of randomisation
4	<ul style="list-style-type: none"> <li>• Guo (2009)</li> <li>• Trend (2002)</li> <li>• Van der Marck (2013)</li> <li>• Wade (2003)</li> </ul>	Exercise was component of multidisciplinary rehabilitation
4	<ul style="list-style-type: none"> <li>• Lee (2015)</li> <li>• Mohr (1996)</li> <li>• Müller (1997)</li> <li>• Ridgel (2016)</li> </ul>	Exercise was combined with an additional treatment (e.g. functional electrical stimulation, psychoeducation)
2	<ul style="list-style-type: none"> <li>• Comella (1994)</li> <li>• Nieuwboer (2007).</li> </ul>	Crossover design: anxiety and depression were not assessed at the end of the first period
2	<ul style="list-style-type: none"> <li>• Clarke (2009)</li> <li>• Sturkenboom (2014)</li> </ul>	Occupational therapy programme, rather than a physical activity intervention
1	<ul style="list-style-type: none"> <li>• Foster (2013)</li> </ul>	Depressive symptoms were not reported at post-intervention and follow-up assessment
1	<ul style="list-style-type: none"> <li>• Gauthier (1987)</li> </ul>	Assessment of psychological well-being
1	<ul style="list-style-type: none"> <li>• Hackney (2007)</li> </ul>	Assessment of morale
1	<ul style="list-style-type: none"> <li>• Lewis (2016)</li> </ul>	Not only PD patients in the sample population
1	<ul style="list-style-type: none"> <li>• Park (2014)</li> </ul>	Delayed-start design: not assessment of anxiety and depression at the end of the first period
1	<ul style="list-style-type: none"> <li>• Rochester (2005)</li> </ul>	Single bout of exercise
1	<ul style="list-style-type: none"> <li>• Stallibrass (2002)</li> </ul>	Alexander technique as intervention, which is considered an educational process rather than a form of exercise
1	<ul style="list-style-type: none"> <li>• Christofletti (2012)</li> </ul>	Published in Portuguese

References of excluded trials

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**Appendix 4.5.** Classification of exercise intensity (adopted from ACSM's, 2006).

Exercise intensity	HRR (%)	HR <sub>max</sub> (%)
Very light	<20	<35
Light	20-39	35-54
Moderate	40-59	55-69
Heavy	60-84	70-89
Very heavy	85-99	90-99
Maximal	100	100

Abbreviations. HR<sub>max</sub>: heart rate maximum; HRR: heart rate reserve




# Appendix 4.6. Exercise characteristics of effective trials on depression.

First author name (year of publication)	Participants	Intervention									
		H&Y stage (All)	Mode of exercise	Description of exercise protocol	Setting	Exercise format	Supervision	Programme duration (weeks)	Frequency (per week)	Session duration (minutes)	Exercise intensity
Cugusi (2015)	1-3	Aerobic training	warm-up main part: Nordic walking cool-down	City park	Group	Supervised	12	2	60	60%-80% HRR	
Hashimoto (2015)	2-4	Dance	Warm-up, main part, cool – down: modern dance using elements from aerobic, jazz, tango and classical ballet	N/A	N/A	N/A	12	1	60	50%-70% HRmax	
King (2015)	2.4 (mean)	Exercise based on the ABC exercise programme	6 stations: tai chi, boxing, pilates, lunges, kayaking, agility course	Rehab. centre	Individual.	Supervised	4	3	60	N/A	
Nadeau (2014)	1.5-2	Aerobic training (speed TT)	warm-up main part: treadmill walking; initial speed at 80% of preferential walking speed ↑ speed by 0.2 km/h per session cool-down	University	Individual.	Supervised	24	3	60	up to 75% HRmax and BP up to 200 mm Hg	
Smania (2010)	3-4	Balance training	10 exercises of 5-10 repetitions grouped in 3 categories: self-destabilisation, externally induced destabilisation, destabilising activities	University	Individual.	Supervised	7	3	50	N/A	
Teixeira- Machado (2015)	2-3	Feldenkrais method- based exercise	Breathing, flexibility, balance and strengthening exercises; position changes; relaxation	Hospital	N/A	Supervised	24	2	60	N/A	

ABC: Agility Boot Camp; CG: comparison group; H&Y: Hoehn and Yahr; HRmax: maximum heart rate; HRR: heart rate reserve; IG: intervention group; Individual.: individualised; N/A: not available; Rehab: rehabilitation; TT: treadmill training.

## Appendix 5.1. Ethical approval for the entire study granted by the HPDA (Greek version).



**ΕΠΙΚΟΥΡΟΣ**  
**Μελέτη, Θεραπεία και Υποστήριξη**  
**Διαταραχών Νόησης και Κίνησης**  
 Αστική μη κερδοσκοπική Εταιρεία

Αθήνα, 25 Μαΐου 2011  
 Αρ. Πρωτ. 12/2011

Αγαπητέ κε Θεόδωρε Χατζηδαμιανέ,

Σας ενημερώνουμε ότι η Επιστημονικής Επιτροπής της Αστικής Μη Κερδοσκοπικής Εταιρείας ΕΠΙΚΟΥΡΟΣ κίνηση, αφού μελέτησε την αίτησή σας


**Εγκρίνει την διεξαγωγή της μελέτης σας με θέμα**

«The effectiveness of a group exercise programme on improving anxiety, depression, quality of life and prevention of falls in Greek elderly population suffering from Parkinson's disease».

Γιατί είναι σύμφωνη με την ηθική δεοντολογία και τους σκοπούς της εταιρείας μας.

Η μελέτη θα διεξαχθεί σε συνεργασία και υπό την αιγίδα της ΕΠΙΚΟΥΡΟΣ κίνηση που σαν κύριο σκοπό στη βελτίωση της ποιότητας ζωής των ατόμων με νόσο του Πάρκινσον και των φροντιστών τους, στην πρόσβαση των ατόμων αυτών σε νέες θεραπευτικές μεθόδους αλλά και στην ενημέρωση και την εκπαίδευση τόσο των ατόμων με τη νόσο, των φροντιστών τους, του κοινού αλλά και της ευρύτερης επιστημονικής κοινότητας.


Εκ μέρους του Διοικητικού Συμβουλίου της ΕΠΙΚΟΥΡΟΣ και πρόεδρος της ΕΠΙΚΟΥΡΟΣ κίνηση  
 Παναγιώτης Ι. Ζήκος



**ΕΠΙΚΟΥΡΟΣ**  
**ΜΕΛΕΤΗ - ΘΕΡΑΠΕΙΑ - ΥΠΟΣΤΗΡΙΞΗ**  
**ΔΙΑΤΑΡΑΧΩΝ ΝΟΗΣΗΣ & ΚΙΝΗΣΗΣ**  
 ΤΡΙΑΝΤΑΦΥΛΛΙΔΗ 40 - ΑΘΗΝΑ  
 ΑΦΜ: 998858340 - ΔΟΥ: ΨΥΧΙΚΟΥ

ΕΠΙΚΟΥΡΟΣ 210-2224466, [www.parkinsonportal.gr](http://www.parkinsonportal.gr), email [info@parkinsonportal.gr](mailto:info@parkinsonportal.gr)

**Appendix 5.2. Ethical approval for the entire study granted by the HPDA (English version).**



**IKOYROS**  
**Study, management and support**  
**of movement and cognition disorders**  
 non political and non profit organisation

Athens 25<sup>th</sup> May 2011  
 Protocol Number: 12/2011

Dear Mr. Theodoros Chatzidamianos,

We would like to inform you that the Scientific Committee of the non-religious, non-political, and non-profit Parkinson's Disease Association of Greece 'Epikouros kinisi' after studying your request

**approves the conduct of your study entitled:**


"The effectiveness of a group exercise programme on improving anxiety, depression, quality of life and prevention of falls in Greek elderly population suffering from Parkinson's Disease"

as it is consistent with ethics and purposes of 'Epikouros kinisi'.

The study will be conducted with cooperation and under the supervision of 'Epikouros kinisi'. 'Epikouros kinisi' is a non-religious, non-political, and non-profit organisation and a member of the European Parkinson's Disease Association (E.P.D.A.). The main aim of our organisation is the improvement of the quality of life of people living with Parkinson's disease and their families and carers; to offer new treatments for management of the disease and provide new information and guidance to Parkinson's Disease patients, their carers, society and scientific community.

On behalf of the board of 'Epikouros' and president of 'Epikouros kinisi'

Panagiotis I. Zikos



**ΕΠΙΚΟΥΡΟΣ**  
 ΑΜΚΕ - ΤΡΙΑΝΤΑΦΥΛΛΙΑΔΗ 40  
 ΑΘΗΝΑ ΑΦΜ 998858340  
 ΔΟΥ Ν. ΨΥΧΙΚΟΥ

Epikouros tel: +30 210 2224466, www.parkinsonportal.gr, e-mail: info@parkinsonportal.gr

**Appendix 5.3. Ethical approval for the 'Step one' (survey) granted by the HPDA.**



**Appendix 5.4.** Invitation e-mail for the online survey (Greek version).**ΕΡΩΤΗΜΑΤΟΛΟΓΙΟ ΓΙΑ ΑΣΘΕΝΕΙΣ ΜΕ ΠΑΡΚΙΝΣΟΝ**

Αγαπητά μέλη της ΕΠΙΚΟΥΡΟΣ κίνηση,

Αν είστε Άτομο με Πάρκινσον (ΑμΠ) ή φροντιστής ΑμΠ σας καλούμε να μας βοηθήσετε ανώνυμα στην σημαντική έρευνα που διεξάγουμε για την νόσο Πάρκινσον στην Ελλάδα. Η έρευνα πραγματοποιείται στο πλαίσιο διδακτορικών σπουδών του κου Θεόδωρου Χατζηδαμιανού στο Μητροπολιτικό Πανεπιστήμιο του Μάντσεστερ, Ηνωμένο Βασίλειο. Αν θέλετε να συμμετάσχετε, σας παρακαλούμε να συμπληρώσετε το ερωτηματολόγιο που βρίσκεται στον παρακάτω σύνδεσμο:

<http://docs.google.com/forms/d/1JYku5P-ItJGvGwVTriSBVCQ0A-HAh0iTptYTive2Rbo/viewform>

Ο χρόνος συμπλήρωσης του ερωτηματολογίου είναι 4 με 20 λεπτά. Η έρευνα αφορά ΜΟΝΟ Άτομα που πάσχουν από Πάρκινσον και μπορεί να συμπληρωθεί και από φροντιστές τους. Στο τέλος του ερωτηματολογίου πατήστε 'Υποβολή' / «submit» ώστε να λάβουμε την απάντησή σας. Σας παρακαλούμε να συμπληρώσετε το ερωτηματολόγιο εντός 30 ημερών.

**Σκοπός**

Σκοπός του ερωτηματολογίου που καλείστε να συμπληρώσετε είναι η διερεύνηση των επιπτώσεων των καθημερινών δραστηριοτήτων και της συναισθηματικής κατάστασης σε ΑμΠ. Τα δεδομένα που θα συλλεχθούν, θα μας βοηθήσουν να κατανοήσουμε τα κύρια προβλήματα που αντιμετωπίζουν τα ΑμΠ στην καθημερινότητα τους, ώστε να σχεδιάσουμε ένα πρόγραμμα θεραπευτικής άσκησης κι εκπαίδευσης, κατάλληλο για την συγκεκριμένη πάθηση.

**Εμπιστευτικότητα πληροφοριών**

Οι απαντήσεις σας και τα προσωπικά σας στοιχεία δεν θα γνωστοποιηθούν πέρα των ερευνητών. Μόνο οι ερευνητές θα έχουν πρόσβαση στο ερωτηματολόγιο που έχετε συμπληρώσει. Η ανωνυμία σας διασφαλίζεται καθ' όλη την διεξαγωγή της έρευνας. Η συμμετοχή σας στη συμπλήρωση του ερωτηματολογίου είναι εθελοντική.

**Δομή ερωτηματολογίου**

Το ερωτηματολόγιο αποτελείται από 5 τμήματα. Το πρώτο τμήμα περιέχει γενικές ερωτήσεις και τα υπόλοιπα ερωτήσεις που αφορούν τις καθημερινές σας δραστηριότητες και τη συναισθηματική σας κατάσταση. Στην ερώτηση στο τέλος του ερωτηματολογίου, μπορείτε να γράψετε επιπλέον σχόλιά για την εμπειρία σας ως ΑμΠ ή φροντιστής ΑμΠ. Σε κάθε περίπτωση, θα πρέπει να είστε ειλικρινείς στις απαντήσεις σας για την συλλογή έγκυρων και αξιόπιστων αποτελεσμάτων.

Για περισσότερες πληροφορίες, παρακαλώ επικοινωνήστε με τον κο Θεόδωρο Χατζηδαμιανό.

Σας ευχαριστούμε για τον χρόνο σας και την συμμετοχή σας.

**Ερευνητική ομάδα:**

Θεόδωρος Χατζηδαμιανός, φυσικοθεραπευτής

Τηλέφωνο: 69470057XX

Ηλεκτρονικό ταχυδρομείο: thchdamianos@yahoo.gr

**Appendix 5.5.** Invitation e-mail for the online survey (English version).**QUESTIONNAIRE FOR PATIENTS WITH PARKINSON'S DISEASE**

Dear members of Epkouros-kinisi,

If you are patient with Parkinson's disease (PD) or carer of a patient with PD, we invite you to take part in our research study about PD in Greek population. The research is part of the doctorate studies of Mr. Theodoros at Manchester Metropolitan University, United Kingdom. If you wish to participate in the study, please complete the online questionnaire at the following link:

[http://docs.google.com/forms/d/1JYku5P\\_ItJGvGwVTriSBVCQ0A-HAh0iTptYTive2Rbo/viewform](http://docs.google.com/forms/d/1JYku5P_ItJGvGwVTriSBVCQ0A-HAh0iTptYTive2Rbo/viewform)

The required time to complete the questionnaire is between 4 and 20 minutes. The study refers only to people suffering from PD and it can be completed by themselves or their carer. At the end of the questionnaire press the 'submit' button to receive your questionnaire. The deadline for the completion of questionnaire is 30 days.

***Objective***

The objective of the questionnaire is the investigation of activities of daily living and psychological well-being in patients with PD. The collection of data will help us to understand the major problems of individuals with PD in their daily life, in order to design an exercise and education programme for this population.

***Confidentiality***

Your answers and all your personal information will be known only to researchers. Only the researchers of the current study will have access to your questionnaire. The anonymity is ensured throughout the survey. Your participation in completing the questionnaire is voluntary.

***Questionnaire structure***

The questionnaire consists of 5 sections. The first section includes general questions for your life and health. The following sections are relevant to your daily activities and your emotional state. At the end of the questionnaire there is an extra question, where you can give us more relevant information about your experience living with PD. In any case, you should be honest in your answers for the collection of valid and reliable data.

For further information please contact Mr. Theodoros Chatzidamianos

Thank you in advance for your assistance!

**Research team**

Theodoros Chatzidamianos, physiotherapist

mobile phone: 69470057XX

e-mail: thchdamianos@yahoo.gr



**Appendix 5.6.** Invitation and consent form for the paper survey (Greek version).

**ΕΠΙΚΟΥΡΟΣ - κίνηση**  
 Ελληνική εταιρεία  
 εθελοντών και ασθενών  
 για την ν. Πάρκινσον

### ΕΡΩΤΗΜΑΤΟΛΟΓΙΟ ΓΙΑ ΑΣΘΕΝΕΙΣ ΜΕ ΝΟΣΟ ΠΑΡΚΙΝΣΟΝ

Αγαπητή κυρία/ αγαπητέ κύριε,

Αν είστε Άτομο με Πάρκινσον (ΑμΠ) ή φροντιστής ΑμΠ σας καλούμε να μας βοηθήσετε ανώνυμα στην σημαντική έρευνα που διεξάγουμε για την νόσο Πάρκινσον στην Ελλάδα. Αυτό μπορεί να γίνει συμπληρώνοντας το ερωτηματολόγιο που θα σας δώσουμε. Η έρευνα πραγματοποιείται στο πλαίσιο διδακτορικών σπουδών του κου Θεόδωρου Χατζηδαμιανού στο Μητροπολιτικό Πανεπιστήμιο του Μάντσεστερ, Ηνωμένο Βασίλειο. Ο χρόνος συμπλήρωσης του ερωτηματολογίου είναι 4 με 20 λεπτά. Η έρευνα αφορά ΜΟΝΟ Άτομα που Πάσχουν από Πάρκινσον και μπορεί να συμπληρωθεί και από φροντιστές τους.

#### **Σκοπός**

Σκοπός του ερωτηματολογίου, που καλείστε να συμπληρώσετε, είναι η διερεύνηση των επιπτώσεων των καθημερινών δραστηριοτήτων και της συναισθηματικής κατάστασης σε ΑμΠ. Τα δεδομένα που θα συλλεχθούν, θα μας βοηθήσουν να κατανοήσουμε τα κύρια προβλήματα που αντιμετωπίζουν τα ΑμΠ στην καθημερινότητα τους, ώστε να σχεδιάσουμε ένα πρόγραμμα θεραπευτικής άσκησης κι εκπαίδευσης, κατάλληλο για την συγκεκριμένη πάθηση.

#### **Εμπιστευτικότητα πληροφοριών**

Οι απαντήσεις σας και τα προσωπικά σας στοιχεία δεν θα γνωστοποιηθούν πέρα των ερευνητών. Μόνο οι ερευνητές θα έχουν πρόσβαση στο ερωτηματολόγιο που έχετε

συμπληρώσει. Η ανωνυμία σας διασφαλίζεται καθ' όλη την διεξαγωγή της έρευνας. Η συμμετοχή σας στη συμπλήρωση του ερωτηματολογίου είναι εθελοντική. Αν τελικά αλλάξετε γνώμη για τη συμμετοχή σας, μπορείτε να αποσυρθείτε όποτε θέλετε εσείς κατά την διάρκεια ή μετά το τέλος της συμπλήρωσης του ερωτηματολογίου.

### **Δομή ερωτηματολογίου**

Το ερωτηματολόγιο αποτελείται από 5 τμήματα. Το πρώτο τμήμα περιέχει γενικές ερωτήσεις και τα υπόλοιπα ερωτήσεις που αφορούν τις καθημερινές σας δραστηριότητες και τη συναισθηματική σας κατάσταση. Στην ερώτηση στο τέλος του ερωτηματολογίου, μπορείτε να γράψετε επιπλέον σχόλιά για την εμπειρία σας ως ΑμΠ ή φροντιστής ΑμΠ. Σε κάθε περίπτωση, θα πρέπει να είστε ειλικρινείς στις απαντήσεις σας για την συλλογή έγκυρων και αξιόπιστων αποτελεσμάτων.

Σας ευχαριστούμε για τον χρόνο σας και την συμμετοχή σας!

### **Ερευνητική ομάδα:**

Παναγιώτης Ζήκος, ειδικός νευρολόγος

Θεόδωρος Χατζηδαμιανός, φυσικοθεραπευτής

### **Επικοινωνία**

Αν θέλετε περισσότερες πληροφορίες μπορείτε να επικοινωνήσετε με τον κο Θεόδωρο Χατζηδαμιανό.

Τηλέφωνο: 69470057XX

Ηλεκτρονικό ταχυδρομείο: thchdamianos@yahoo.gr

### **ΔΗΛΩΣΗ ΣΥΓΚΑΤΑΘΕΣΗΣ**

Ενημερώθηκα για την μελέτη και έχω καταλάβει το σκοπό της. Αποφάσισα να συμμετάσχω εθελοντικά γνωρίζοντας ότι οι πληροφορίες που θα δώσω θα μείνουν απόρρητες και ότι μπορώ να αποσυρθώ όποτε θέλω.

**Υπογραφή συμμετέχοντα:** .....

**Appendix 5.7.** Invitation and consent form for the paper survey (English version).

**ΕΠΙΚΟΥΡΟΣ - κίνηση**  
 Ελληνική εταιρεία  
 εθελοντών και ασθενών  
 για την ν. Πάρκινσον

## **QUESTIONNAIRE FOR PATIENTS WITH PARKINSON'S DISEASE**

Dear Madame/Sir,

If you are patient with Parkinson's disease (PD) or carer of a patient with PD, we invite you to take part in our research study about PD in Greek population. The research is part of the doctorate studies of Mr. Theodoros at Manchester Metropolitan University, United Kingdom. If you wish to participate in the study, please complete the questionnaire that will give you. The required time to complete the questionnaire is between 4 and 20 minutes. The study refers only to people suffering from PD and it can be completed by themselves or their carer.

### ***Objective***

The objective of the questionnaire is the investigation of activities of daily living and psychological well-being in patients with PD. The collection of data will help us to understand the major problems of individuals with PD in their daily life, in order to design an exercise and education programme for this population.

### ***Confidentiality***

Your answers and all your personal information will be known only to researchers. Only the researchers of the current study will have access to your questionnaire. The anonymity is ensured throughout the survey. Your participation in completing the questionnaire is voluntary.

**Questionnaire structure**

The questionnaire consists of 5 sections. The first section consists of general questions for your life and health. The following sections are relevant to your daily activities and your emotional state. At the end of the questionnaire there is an extra question, where you can give us more relevant information about your experience living with PD. In any case, you should be honest in your answers for the collection of valid and reliable data.

Thank you in advance for your time!

**Research team:**

Panagiotis Zikos, neurologist

Theodoros Chatzidamianos, physiotherapist

**Contact details**

For further information, please contact Mr. Theodoros Chatzidamianos

Mobile phone: 69470057XX

e-mail: thchdamianos@yahoo.gr

**CONSENT FORM**

I confirm that I have read and understood the information sheet for the current study. I decided to participate voluntary, as the information I give will remain confidentially.

**Participant's signature:** .....

**Appendix 5.8.** Items of the ‘feedback questionnaire’ for the pilot work.

Number	Question
01	How much time did you take to complete the questionnaire?
02	Were the instructions understood? <input type="checkbox"/> Yes <input type="checkbox"/> No
	If you answered ‘no’ to the previous question, please explain the reason(s) the instructions were not understood.
03	Were all the questions understood? <input type="checkbox"/> Yes <input type="checkbox"/> No
	If you answered ‘no’ to the previous question, please explain the reason(s) the question(s) were not understood.
04	Did you answer all the questions? <input type="checkbox"/> Yes <input type="checkbox"/> No
	If you answered ‘no’ to the previous question, please explain the reason(s) you didn’t answer all the questions.
05	Is there any other activity of your daily living, that has been affected due to Parkinson’s disease, and it is not included in the questionnaire?  <input type="checkbox"/> Yes <input type="checkbox"/> No
	If you answered ‘no’ to the previous question, please specify the affected activity.

06	Was the questionnaire easy to complete it? <input type="checkbox"/> Yes <input type="checkbox"/> No
	If you answered know to the previous question, please indicate the reason(s).
07	Was the questionnaire well-designed? <input type="checkbox"/> Yes <input type="checkbox"/> No
08	<p>Please mark the questionnaire.</p> <p style="text-align: center;"><i>no good</i> 0 1 2 3 4 5 6 7 8 9 10 <i>excellent</i></p>
09	<p>If you have any additional comments or ideas, that will help us to improve the questionnaire, please write them in the provided space.</p>

**Appendix 8.1.** Criteria of the Article 4 of the 'Hellenic General Specifications for the authorisation of a fitness centre' (Government Newspaper of the Hellenic Republic, 2006).

The criteria of the Article 4 are listed as follows:

- Each trainer requires at least five square metres (m<sup>2</sup>) for exercise.
- Height of the exercise room at least 2.60 metres.
- Adequate natural and/or artificial lighting
- Adequate natural and/or artificial ventilation
- Slip resistant coating to the entire surface of the floor
- Fire safety
- First aid kit

Appendix 8.2. Brochure to reach patients for the study (in Greek).

**ΠΡΟΓΡΑΜΜΑ**  
**“ΕΠΙΚΟΥΡΟΣ - ΚΟΙΝΟΤΗΤΕΣ ΠΑΡΚΙΝΣΟΝ”**

Ένα φιλόδοξο πρόγραμμα,  
που θα ανακουφίσει τις οικογένειες και τους  
ανθρώπους με νόσο Πάρκινσον  
ξεκίνησε στον Δήμο μας.



Εγγραφείτε **δωρεάν** μέλη στη  
**Κοινότητα Πάρκινσον ΕΠΙΚΟΥΡΟΣ κίνηση**  
του δήμου μας στο **210 222 44 66**  
(10:00 - 18:00 αστική χρέωση)



**ΕΠΙΚΟΥΡΟΣ - κίνηση**  
Ελληνική εταιρεία  
εθελοντών και ασθενών  
για την ν. Πάρκινσον



Το πρόγραμμα είναι πρωτοβουλία της Ελληνικής Εταιρείας εθελοντών και ασθενών για την νόσο Πάρκινσον «ΕΠΙΚΟΥΡΟΣ κίνηση» και σαν σκοπό έχει την δημιουργία μιας τοπικής Κοινότητας ατόμων με Πάρκινσον σε κάθε δήμο που συμμετέχει, σε μια κοινή προσπάθεια να ενημερωθούν υπεύθυνα και να λάβουν μια όσο γίνεται πιο ολοκληρωμένη θεραπεία της νόσου.

Είναι γεγονός ότι η νόσος Πάρκινσον είναι σύνθετη ασθένεια. Η εξέλιξη της είναι προοδευτική και επηρεάζει την κίνηση, την σκέψη και το συναίσθημα. Η επίπτωση της είναι σημαντική και στην οικογένεια, όπου ο σύντροφος επωμίζεται ένα μεγάλο βάρος της φροντίδας. Ας μην ξεχνάμε ότι η Πάρκινσον οδηγεί σε κινητική ή και νοητική «αναπηρία».

Η «ΕΠΙΚΟΥΡΟΣ κίνηση» διαπίστωσε ότι στην εποχή μας ένα μεγάλο μέρος των Ατόμων με Πάρκινσον δεν έχει την δυνατότητα πρόσβασης σε αξιοπιστες υπηρεσίες που να παρέχουν μια ολοκληρωμένη φροντίδα τόσο του ασθενή όσο και του φροντιστή.

Το πρόγραμμα «ΕΠΙΚΟΥΡΟΣ- ΚΟΙΝΟΤΗΤΕΣ ΠΑΡΚΙΝΣΟΝ» φιλοδοξεί να προσφέρει δωρεάν υποστήριξη των φροντιστών & των πασχόντων στον χώρο στον οποίο ζουν.

Ευχαριστούμε τον αντιδήμαρχο κοινωνικής αλληλεγγύης του δήμου μας για την αμέριστη υποστήριξη.



Με εκτίμηση,  
πρόεδρος της **ΕΠΙΚΟΥΡΟΣ κίνηση**  
Ζήκος Ι. Παναγιώτης - Νευρολόγος

**Εγγραφείτε ΔΩΡΕΑΝ μέλη στην Κοινότητα Πάρκινσον**

ΕΠΙΚΟΥΡΟΣ κίνηση του δήμου μας και συμμετέχετε σε όποια δραστηριότητα έχετε ανάγκη.

Υπάρχουν διαρκώς δράσεις όπως:

- **Εξέταση αξιολόγηση** από εξειδικευμένη ομάδα επιστημόνων.
- **Ομαδικά προγράμματα φυσικοθεραπείας** ατόμων με νόσο Πάρκινσον.
- **Ομάδες ψυχολογικής υποστήριξης** για τους φροντιστές των ασθενών.
- **Σχολείο Φροντιστών** ατόμων με νόσο Πάρκινσον
- **Μηνιαίες συναντήσεις των μελών της Κοινότητας Πάρκινσον ΕΠΙΚΟΥΡΟΣ** κίνηση του δήμου μας, με στόχο την ενημέρωση και την κοινωνικοποίηση.
- **Γραμμή Ψυχολογικής Βοήθειας Πάρκινσον**

**90 11 40 40 34** (10.00 -14.00, Χρέωση από σταθ. 1,23€/1')

**Εγγραφή στις Κοινότητες Πάρκινσον ΕΠΙΚΟΥΡΟΣ κίνηση**

**στο τηλέφωνο:**

**Γραμμή Βοήθειας Πάρκινσον ΕΠΙΚΟΥΡΟΣ κίνηση**

**210 222 44 66**

(10:00 -18:00 αστική χρέωση)

email: epikouros.kinisi@outlook.com

Πληροφορίες

**[www.parkinsonportal.gr](http://www.parkinsonportal.gr)**

Facebook: EPIKOYROS.kinesis



Σχετικά με την ΕΠΙΚΟΥΡΟΣ-κίνηση

Η ΕΠΙΚΟΥΡΟΣ-κίνηση, η Ελληνική εταιρεία εθελοντών και ασθενών με νόσο Πάρκινσον, είναι εταιρεία μη κερδοσκοπικού χαρακτήρα που ιδρύθηκε το 2006.

Αριθμεί περισσότερα από 1350 μέλη σε όλη την Ελλάδα, τα οποία είναι Άτομα με ν. Πάρκινσον, φροντιστές, επιστήμονες υγείας και εθελοντές.

Οι σκοποί της ΕΠΙΚΟΥΡΟΣ - κίνηση είναι η βελτίωση της ποιότητας ζωής των μελών, η διευκόλυνση της πρόσβασης σε σύγχρονες θεραπευτικές μεθόδους, η ενημέρωση και εκπαίδευση σχετικά με την νόσο, η προαγωγή της επιστημονικής έρευνας για την θεραπεία και την κατανόηση της ν. Πάρκινσον.

Η ΕΠΙΚΟΥΡΟΣ-κίνηση έχει δράση και στην Ευρώπη αναπτύσσοντας σχέσεις με άλλες εταιρείες ιδίου σκοπού.

Το 2014 ο πρόεδρος της ΕΠΙΚΟΥΡΟΣ-κίνηση, κος Ζήκος Παναγιώτης, εξελέγη μέλος του Διοικητικού συμβουλίου της EPDA - European Parkinson's Disease Association.

Επικοινωνία:

**Γραμμή Βοήθειας Πάρκινσον ΕΠΙΚΟΥΡΟΣ κίνηση**

**210 222 44 66**

(αστική χρέωση 10.00- 18.00)

**Γραμμή Ψυχολογικής Βοήθειας Πάρκινσον**

**90 11 40 40 34** (10.00- 14.00)

(Χρέωση από σταθ. 1,23€/1', κιν.1,57€/1',  
γραμμή παραπόνων 214-2148020, MEDIATEL)

**www.parkinsonportal.gr**


email info@parkinsonportal.gr



EPIKOYROS.kinesis

Appendix 8.3. Poster to reach patients for the study (in Greek).

**ΠΡΟΓΡΑΜΜΑ**  
**"ΕΠΙΚΟΥΡΟΣ - ΚΟΙΝΟΤΗΤΕΣ ΠΑΡΚΙΝΣΟΝ"**



**ΕΠΙΚΟΥΡΟΣ - κίνηση**  
 Ελληνική εταιρεία  
 εθελοντών και ασθενών  
 για την ν. Πάρκινσον

Εγγραφείτε **ΔΩΡΕΑΝ** στην **Κοινότητα Πάρκινσον**  
**ΕΠΙΚΟΥΡΟΣ κίνηση** του δήμου μας  
 στο **210 222 44 66** (10.00 - 18.00 αστική χρέωση)


Συμμετέχετε σε δράσεις όπως:


- Εξέταση αξιολόγησης από εξειδικευμένη ομάδα επιστημόνων.
- Ομαδικά προγράμματα φυσικοθεραπείας
- Ομάδες ψυχολογικής υποστήριξης
- Σχολείο Φροντιστών
- Μηνιαίες συναντήσεις των μελών της Κοινότητας Πάρκινσον

**ΕΠΙΚΟΥΡΟΣ κίνηση** του δήμου μας.

- Γραμμή Ψυχολογικής Βοήθειας Πάρκινσον **90 11 40 40 34**  
 (10.00 - 14.00, Χρέωση από σταθ. 1,23€/1')

- Με την αμέριστη υποστήριξη του αντιδημάρχου επί θεμάτων υγείας του δήμου μας.



Πληροφορίες:  
 Γραμμή Βοήθειας Πάρκινσον  
**ΕΠΙΚΟΥΡΟΣ κίνηση**  
**210 222 44 66**  
[www.parkinsonportal.gr](http://www.parkinsonportal.gr)  
 [EPIKOYROS.kinesis](https://www.facebook.com/epikouros.kinesis)

**Appendix 8.4.** Participant Information Sheet' (Greek version).**ΕΝΤΥΠΟ ΕΝΗΜΕΡΩΣΗΣ**

Η παρούσα έρευνα στοχεύει στην διερεύνηση της αποτελεσματικότητας ενός ομαδικού προγράμματος άσκησης και εκπαίδευσης σε Άτομα με νόσο Πάρκινσον (ΑμΠ) στους δείκτες κατάθλιψης και άγχους, στην κινητικότητα, στην ποιότητα ζωής και στην αναπνευστική λειτουργία.

Σας προσκαλούμε να λάβετε μέρος στην έρευνά μας. Προτού όμως αποφασίσετε για την συμμετοχή σας, είναι σημαντικό να διαβάσετε προσεκτικά το παρόν φυλλάδιο, ώστε να καταλάβετε τον σκοπό της έρευνας και την όλη διαδικασία.

**1. Ποιος είναι ο σκοπός της έρευνας;**

Η νόσος του Πάρκινσον είναι η δεύτερη πιο εκφυλιστική πάθηση σε παγκόσμιο επίπεδο. Τα κινητικά συμπτώματα της νόσου ευθύνονται για τον αυξημένο αριθμό πτώσεων, που είναι δυο φορές μεγαλύτερος σε σχέση με τον γενικό πληθυσμό, και για τους σχετικούς τραυματισμούς. Τα μη κινητικά συμπτώματα της νόσου είναι λιγότερο γνωστά στους ασθενείς. Η κατάθλιψη και οι αγχώδεις διαταραχές είναι από τα πιο συχνά μη κινητικά συμπτώματα της νόσου, με διπλάσια συχνότητα εμφάνισης συγκριτικά με τον γενικό πληθυσμό. Όλα αυτά τα συμπτώματα επιφέρουν αρνητικές επιπτώσεις στην ποιότητα ζωής των ΑμΠ.

Ένα πρόγραμμα θεραπευτικής άσκησης και εκπαίδευσης, συμπληρωματικό της φαρμακευτικής αγωγής, θα μπορούσε να επωφελήσει τα ΑμΠ. Τα αποτελέσματα προηγούμενων ερευνών αποδεικνύουν ότι η ομαδική άσκηση σε υγιή πληθυσμό είναι αποτελεσματική για τη βελτίωση της μυϊκής δύναμης, ισορροπίας, ποιότητας ζωής και για τη μείωση του αριθμού των πτώσεων. Επιπλέον, πιστεύεται ότι η άσκηση συνεισφέρει στη μείωση των συμπτωμάτων κατάθλιψης και άγχους.

## **2. Γιατί προσκλήθηκα να συμμετάσχω στην έρευνα;**

Έχετε προσκληθεί, γιατί έχετε διαγνωστεί με τη νόσο του Πάρκινσον και με συμπτώματα κατάθλιψης. Επίσης, δεν πάσχετε από κάποια σοβαρή μυοσκελετική πάθηση, καρδιαγγειακή πάθηση ή άλλη νευρολογική πάθηση που να επηρεάζει την συμμετοχή σας στο πρόγραμμα άσκησης.

## **3. Πρέπει να λάβω μέρος στην έρευνα;**

Αυτό εξαρτάται από εσάς. Αν δεν θέλετε να συμμετάσχετε, απλώς δεν υπογράφετε το έντυπο συγκατάθεσης. Επιπλέον, μπορείτε να αποχωρήσετε από την έρευνα όποια στιγμή θέλετε.

## **4. Τι θα συμβεί αν λάβω μέρος;**

Αν θέλετε να λάβετε μέρος στην έρευνα, απλά συμπληρώνετε το έντυπο συγκατάθεσης και το επιστρέφετε σε εμάς. Έπειτα θα λάβετε ενημέρωση για την συμμετοχή σας. Προηγουμένως ένας νευρολόγος θα σας εξετάσει για να πιστοποιήσει ότι είστε ικανός να συμμετάσχετε στην έρευνα και ότι έχετε συμπτώματα κατάθλιψης, καθώς αυτό είναι το βασικό μας κριτήριο.

## **5. Τι θα συμβεί έπειτα;**

Αν πληροίτε όλα τα κριτήρια, θα συμμετάσχετε στην έρευνα. Τις περισσότερες φορές δεν γνωρίζουμε αν μια θεραπεία είναι ωφέλιμη ή όχι. Γι' αυτό τον λόγο θα χωριστείτε τυχαία σε μια από τις δύο ομάδες της έρευνας: ομάδα θεραπευτικής άσκησης και εκπαίδευσης, και ομάδα σύγκρισης.

Τα μέλη της πρώτης ομάδας θα χωριστούν σε επιπλέον υπο-ομάδες των 5 ή 6 ατόμων. Θα συμμετάσχουν σε ένα ομαδικό πρόγραμμα άσκησης και εκπαίδευσης σε κλειστό χώρο. Η διάρκεια του προγράμματος θα είναι 8 εβδομάδες, με δύο θεραπείες τη βδομάδα διάρκειας μιας ώρας. Το πρόγραμμα άσκησης θα περιλαμβάνει μια ποικιλομορφία

ασκήσεων, όπως διατάσεις, βάδιση και ενδυνάμωση. Το όλο πρόγραμμα θα πραγματοποιηθεί σε πέντε δήμους της πρωτεύουσας.

Η ομάδα σύγκρισης θα συμμετάσχει σε ένα ατομικό πρόγραμμα άσκησης στο σπίτι για το ίδιο χρονικό διάστημα. Η ερευνητική ομάδα θα επικοινωνεί μαζί σας μια φορά τη βδομάδα καθ' όλη την περίοδο της έρευνας.

Μετά το τέλος των 8 εβδομάδων, όλοι οι συμμετέχοντες για 3 μήνες θα συμμετάσχουν σ' ένα ατομικό πρόγραμμα άσκησης στο σπίτι. Τέλος, όλοι οι συμμετέχοντες θα εξεταστούν τρεις φορές από την ερευνητική ομάδα: στην αρχή της έρευνας, μετά το πρόγραμμα άσκησης 8 εβδομάδων, και τρεις μήνες έπειτα.

#### **6. Τι θα γίνει με τη φαρμακευτική μου αγωγή κατά την διάρκεια της έρευνας;**

Καθ' όλη την διάρκεια της έρευνας θα συνεχίζετε να παίρνετε κανονικά τα φάρμακά σας.

#### **7. Πρέπει να πληρώσω για την συμμετοχή μου;**

Όχι. Η συμμετοχή σας είναι εθελοντική και δωρεάν.

#### **8. Ποια θα είναι τα πιθανά οφέλη της συμμετοχής μου;**

Πολύ πιθανόν να βελτιώσετε την ισορροπία σας, την ποιότητα ζωή σας, την αναπνευστική σας λειτουργία και να μειωθεί ο αριθμός των πτώσεων. Επίσης τα συμπτώματα κατάθλιψης και άγχους πιθανόν να υποχωρήσουν.

#### **9. Ενδέχεται να υπάρξουν κάποιες παρενέργειες;**

Τα προγράμματα θεραπευτικής άσκησης είναι γενικά ασφαλή και προτείνονται σε ΑμΠ. Για να είμαστε σίγουροι, ένας γιατρός θα σας εξετάσει προτού λάβετε μέρος. Οι

φυσικοθεραπευτές που θα σας διδάσκουν τις ασκήσεις έχουν εμπειρία σε αυτό το κομμάτι και έχουν δουλέψει με ΑμΠ. Επίσης, αν παρατηρηθούν μερικά συμπτώματα κατά την διάρκεια της άσκησης, όπως ζαλάδα, θα γίνει διακοπή της άσκησης. Αν αποφασίσετε τελικά να λάβετε μέρος στην έρευνα, πρέπει να έχετε υπόψην το χρόνο που απαιτείται να αφιερώνετε εβδομαδιαίως για την παρέμβαση, αλλά και την συνολική διάρκεια της έρευνας (περίπου 5 μήνες).

#### **10. Υπάρχουν κάποιοι περιορισμοί;**

Για να ασκηθείτε πρέπει να φοράτε αθλητικά ρούχα και παπούτσια. Το κάπνισμα και το φαγητό απαγορεύονται 2 ώρες πριν την άσκηση.

#### **11. Η συμμετοχή μου θα είναι εμπιστευτική;**

Η συμμετοχή σας θα είναι εμπιστευτική και το όνομά σας δεν θα δημοσιευθεί. Οι προσωπικές σας πληροφορίες θα σφραγιστούν σ' ένα αρχείο, στο οποίο θα έχει πρόσβαση μόνο η ερευνητική ομάδα. Σ' όλα τα έγγραφα το όνομα σας θα αντικατασταθεί από έναν κωδικό.

#### **12. Και αν αποφασίσω στη μέση της έρευνας να αποχωρήσω;**

Μπορείτε να αποχωρήσετε από την έρευνα οποιαδήποτε στιγμή, αν επιθυμείτε. Μπορείτε να αναφέρετε προαιρετικά τον λόγο της αποχώρησής σας.

#### **13. Τι γίνεται αν υπάρξει οποιοδήποτε πρόβλημα;**

Σε αυτή την περίπτωση μπορείτε να αναφέρετε το πρόβλημα σας τηλεφωνικά στην Επίκουρος-κίνηση, που είναι μέλος του ευρωπαϊκού συνδέσμου για την νόσο του Πάρκινσον.



**14. Ο προσωπικός μου ιατρός πρέπει να ενημερωθεί για την συμμετοχή μου στην έρευνα;**

Ο γιατρός σας πρέπει να ενημερωθεί από εσάς για την συμμετοχή σας στην έρευνα και να σας δώσει έγκριση.

**15. Πώς θα χρησιμοποιηθούν οι πληροφορίες που θα πάρετε από μένα;**

Τα συνολικά, και όχι τα ατομικά αποτελέσματα της έρευνας θα δημοσιευθούν στην διδακτορική διατριβή και σε κάποιο επιστημονικό περιοδικό υγείας.

**16. Ποιος διοργανώνει και χρηματοδοτεί την παρούσα έρευνα;**

Ο κος Θεόδωρος Χατζηδαμιανός είναι ο συντονιστής της παρούσας έρευνας. Είναι διδακτορικός φοιτητής στο Μητροπολιτικό Πανεπιστήμιο του Μάντσεστερ, και έχει κερδίσει υποτροφία από το ΙΚΥ για τις σπουδές του.

**17. Από ποιον έχει λάβει έγκριση η έρευνα;**

Η παρούσα έρευνα έχει εγκριθεί από την επιτροπή ηθικής του Μητροπολιτικού πανεπιστημίου του Μάντσεστερ και την 'Επίκουρος-κίνηση'.

**18. Επικοινωνία για επιπλέον πληροφορίες.**

Για περισσότερες πληροφορίες σχετικά με την παρούσα έρευνα, μπορείτε να επικοινωνήσετε με τον κο Θεόδωρο Χατζηδαμιανό.

Κινητό τηλέφωνο: 694 700 57 XX

Ηλεκτρονικό ταχυδρομείο: thchdamianos@yahoo.gr

**Σας ευχαριστούμε που διαβάσατε το παρόν έντυπο. Παρακαλείσθε να το κρατήσετε. Αν συμφωνείτε να συμμετάσχετε στην έρευνα, συμπληρώστε το έντυπο συγκατάθεσης και ένα φωτοαντίγραφο αυτού θα σας δοθεί.**

**Appendix 8.5. Participant Information Sheet' (English version).****PATIENT INFORMATION SHEET**

This study is about the investigation of the effects of a group-based exercise and educational programme on depression and anxiety, motor function, quality of life and respiratory function in individuals suffering from Parkinson's disease (PD).

We are inviting you to take part in this research study. Before you decide whether to participate or not it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and to decide whether or not you wish to be involved.

**1. What is the purpose of the study?**

PD is currently the second most common neurodegenerative disease. The motor symptoms of the disease often contribute to an increased number of falls, which is higher compared to healthy individuals, and a greater incidence of fall-related injuries. In addition, the non-motor symptoms of the disease are less known to the patients. Anxiety and depressive symptoms are some of the non-motor symptoms of the disease, which are twice higher in PD sufferers compared the general healthy population. Both the increased frequency of falls and the high levels of anxiety and depression have negative impacts on patients' quality of life.

An exercise and educational programme, in conjunction with pharmacological therapy, might be effective in individuals suffering from PD. The results of previous studies in healthy population indicate that group exercise programmes are effective to improve muscle strength and balance, to reduce the risk of falls and to improve quality of life. Furthermore, it is believed that exercise is associated with lower depression and anxiety scores.

## **2. Why have I been invited to participate?**

You have been chosen because you have been diagnosed with PD and depressive symptoms; and you are not suffering from severe musculoskeletal, uncontrolled cardiovascular or other neurological diseases.

## **3. Do I have to take part?**

It is up to you to decide whether or not to take part. If you do not wish to participate, you do not have to do anything in response to this request. Moreover, you are free to withdraw from the study at any time.

## **4. What will happen to me if I take part?**

If you are happy to participate in the research, you should sign the consent form and return it to us. When we receive this, we will contact you to discuss your participation in the study. A doctor will examine you to ensure that you could participate and whether you are suffering from depressive symptoms, as only patients suffering from depressive symptoms will take part in this study.

## **5. What will happen next?**

Whether you fulfill the criteria, you will participate in this study. Sometimes we don't know whether a treatment is helpful or not. To find out, we need to make comparisons between different groups. To do this we will randomly allocate you to one of the following groups: (i) exercise and educational group and (ii) comparison group.

The members of the first group will be divided into small subgroups of five to six participants and will participate in an indoor group-based exercise and educational programme. The length of the training period will be eight weeks. The duration of each session will be one hour and the frequency will be twice a week. The programme will

include a variety of exercises, such as stretching, walking, balance and strengthening exercises. The exercise programme will be held at five municipalities of Athens.

The comparison group will participate in an individualised home-based exercise programme. The research team will monitor the patient's well-being once a week through telephone calls for the entire period of study.

After the end of the eight-week period, the participants of both groups will follow a home-based individualised exercise programme for three months. The subjects will be assessed three times: at the entry of the study, at the end of the eight-week exercise programme and three months after the ending of the exercise programme.

#### **6. What about my medication during the study period?**

All the individuals will continue taking their usual care medication during the whole study period.

#### **7. Expenses and payments.**

You do not have to pay to participate in this study.

#### **8. What are the possible benefits of taking part?**

There is possibility to improve your balance, levels of depression and anxiety, quality of life and respiratory function; and minimise the fall risk.

#### **9. What are the possible risks and disadvantages of taking part?**

Exercise programmes are generally safe and recommended to patients with PD. A doctor will examine you before taking part to the study to minimise any possible risk of injury. The

instructor of the exercise and the assistant physiotherapists have experience in therapeutic exercise on PD population. When something will happen unexpectedly during the exercise, such as dizziness or paleness, the exercise will be stopped immediately. If you decide to take part as a volunteer, you should think the weekly time involved and the total duration of the study.

#### **10. Are there any limitations?**

Whether you are selected on the exercise programme group, you should be dressed sportswear. Furthermore, you should avoid smoking and eating at least two hours before the start of each session.

#### **11. Will my taking part be kept confidential?**

All patient information will be stored on password protected computer databases or in locked filing cabinets. You will be allocated a study number, and staff not directly involved with you will know you only by this number. When the results of the study will be reported, individuals who have taken part will not be identified in any way.

#### **12. What if I change my mind about taking part?**

If you decide to take part you are still free to withdraw at any time and without giving a reason. However, it will be useful for us to know the reason of your withdraw.

#### **13. What if there is a problem?**

If there is any problem, you can contact 'Epikouros-kinisi', which is a member of the European Parkinson's Disease Association, and report it.

**14. Will my GP be informed of my involvement in the study?**

With your consent, your GP will be notified of your participation in this study.

**15. How will the information I provide be used?**

We plan to publish the results in a health journal and in the PhD dissertation of the researcher, so others can read about and learn from the results of the study.

**16. Who is organising and funding the research?**

The researcher, Mr. Theodoros Chatzidamianos, is conducting the research as a PhD student at the Department of Physiotherapy, of School of Health, Psychology and Social Care at Manchester Metropolitan University. He has earned a scholarship by the IKY for the conduction of this project.

**17. Who has reviewed this study?**

The research has been approved by the University Research Ethics Committee, Manchester Metropolitan University and the Hellenic Parkinson's Disease Association 'Epikouros-kinisi'.

**18. Contact for further Information**

If you require more information about this study please contact Mr. Theodoros Chatzidamianos.

Telephone number: 694 700 57 XX

e-mail: thchdamianos@yahoo.gr

**Thank you for reading this.**

**Please keep this information sheet.**

**If you agree to enter the study, please sign the consent form and we will return a copy to you.**



## Appendix 8.6. Informed Consent Form (Greek version).

**ΕΝΤΥΠΟ ΣΥΓΚΑΤΑΘΕΣΗΣ**

‘Η αποτελεσματικότητα ενός ομαδικού προγράμματος άσκησης και εκπαίδευσης στην κοινότητα Ελλήνων ασθενών με νόσο Πάρκινσον και κατάθλιψη’

- Έχω διαβάσει το ενημερωτικό φυλλάδιο για την παρούσα έρευνα και όλες οι απορίες μου έχουν απαντηθεί.
- Η συμμετοχή μου είναι εθελοντική και μπορώ να αποχωρήσω από την έρευνα όποια στιγμή επιθυμώ.
- Συμφωνώ ότι μπορεί να γίνει βιντεοσκόπηση και φωτογράφιση, χωρίς όμως να εμφανίζονται τα χαρακτηριστικά του προσώπου μου.
- Συμφωνώ ότι τα δεδομένα θα φυλαχθούν (η φύλαξη θα είναι ανώνυμη) για την πραγματοποίηση της έρευνας.
- Συμφωνώ να λάβω μέρος στην παρούσα έρευνα.

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Όνομα συμμετέχοντα

Ημερομηνία

Υπογραφή

---

Όνομα ερευνητή

Ημερομηνία

Υπογραφή

**Appendix 8.7.** Informed Consent Form (English version).**PARTICIPANT CONSENT FORM**

'The effectiveness of a community-based exercise and educational programme on depression in Greek population with Parkinson's disease'

- I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions.
- I understand that my participation is voluntary and that I am free to withdraw at any time.
- I agree that video recording and photos can be used without reveal my facial features
- I agree that my data gathered in this study will be stored (after it has been anonymised) in a specialist data centre for the conduction of the study.
- I agree to take part in the present study.

---

Name of Participant

Date

Signature

---

Name of Researcher

Date

Signature

**Appendix 8.8.** Description of the Hospital Anxiety and Depression Scale (HADS)

The HADS has 14 items; seven of which address depression, and seven anxiety. Questions related to anxiety are marked with A; whereas questions related to depression with D. (Zigmond and Snaith 1983). The individuals respond to the question in relation to how they felt the last week (Snaith, 2003). Each item has four graded response options on a Likert scale, scored from zero to three. Depressive symptoms are rated separately from anxiety symptoms. The total score of each subscale ranges from 0 to 21 points, with higher scores reflecting greater levels of anxiety and depression. Scores for each subscale could be categorised as follows: normal (0-7), mild (8-10), moderate (11-14), and severe (15-21) (Zigmond and Snaith 1983). However, some researchers also calculate the total HADS score (0-42) as a measure of total psychological distress, due to the frequent difficulty in distinguishing between anxiety and depression in clinical settings (Roberts et al., 2001). In the current study, the HADS was completed by the participants, as it is a self-report instrument.

## Appendix 8.9. Hospital Anxiety and Depression Scale (HADS) (Greek version)

**Νοσοκομειακή Κλίμακα Κατάθλιψης και Άγχους (HADS)**

Αυτό το ερωτηματολόγιο είναι σχεδιασμένο ώστε να βοηθήσει τον κλινικό ιατρό σας να γνωρίσει πώς αισθάνεστε. Διαβάστε κάθε ερώτημα και υπογραμμίστε με X την απάντηση η οποία είναι πλησιέστερη στα συναισθήματά σας της προηγούμενης εβδομάδας. Πρέπει να επιλέξετε μία απάντηση από τις τέσσερις πιθανές επιλογές κάθε ερώτησης. Μην πάρετε πολύ χρόνο για να απαντήσετε, η άμεση ανταπόκριση είναι προτιμότερη.

Όνομα: .....

Ημερομηνία: .....

<b>A.1</b>	<b>Νιώθω ανήσυχος ή τρομαγμένος:</b>	
	Τον περισσότερο καιρό	3
	Πολύ καιρό	2
	Από καιρό σε καιρό, περιστασιακά	1
	Καθόλου	0

<b>D.1</b>	<b>Εξακολουθώ να απολαμβάνω τα πράγματα που συνήθιζα να απολαμβάνω:</b>	
	Σαφέστατα, στον ίδιο βαθμό	0
	Όχι στον ίδιο βαθμό	1
	Λίγο μόνο	2
	Καθόλου	3

<b>A.2</b>	<b>Αντιμετωπίζω κάποιο συναίσθημα φόβου σαν να πρόκειται κάτι τρομακτικό να συμβεί:</b>	
	Ακριβώς, μάλιστα σε σοβαρό βαθμό	3
	Ναι, αλλά όχι τόσο σοβαρά	2
	Ελάχιστα, αλλά δεν μ' ανησυχεί	1
	Καθόλου	0

<b>D.2</b>	<b>Μπορώ να γελάω και να βλέπω την χαρωπή όψη των πραγμάτων:</b>	
	Βεβαίως, έτσι όπως πάντα μπορούσα	0
	Μάλλον όχι τόσο, όπως στο παρελθόν	1
	Σίγουρα όχι τώρα τόσο πολύ	2
	Καθόλου	3

<b>A.3</b>	<b>Ανήσυχες σκέψεις περνούν από το μυαλό μου:</b>	
	Πάρα πολύ καιρό	3
	Πολύ καιρό	2
	Όχι τόσο συχνά	1
	Πολύ λίγο	0

<b>D.3</b>	<b>Νιώθω κεφάλτος:</b>	
	Ποτέ	3
	Όχι συχνά	2
	Μερικές φορές	1
	Τον περισσότερο καιρό	0

<b>A.4</b>	<b>Μπορώ να κάθομαι άνετα και να νιώθω χαλαρωμένος:</b>	
	Ακριβώς	0
	Συνήθως	1
	Όχι συχνά	2
	Καθόλου	3

<b>D.4</b>	<b>Νιώθω σαν να έχουν πέσει οι ρυθμοί μου:</b>	
	Σχεδόν όλο τον καιρό	3
	Πολύ συχνά	2
	Μερικές φορές	1
	Καθόλου	0

<b>A.5</b>	<b>Αντιμετωπίζω κάποιο συναίσθημα φόβου σαν να έχω «πεταλούδες» στο στομάχι μου:</b>	
	Καθόλου	0
	Περιστασιακά	1
	Αρκετά συχνά	2
	Πολύ συχνά	3

<b>D.5</b>	<b>Έχασα το ενδιαφέρον για την εμφάνισή μου:</b>	
	Ακριβώς	3
	Δεν τη φροντίζω όσο θα έπρεπε	2
	Ίσως δεν τη φροντίζω όσο θα έπρεπε	1
	Την φροντίζω όπως πάντοτε	0

<b>A.6</b>	<b>Νιώθω νευρικός και ανήσυχος σαν να πρέπει συνέχεια να κινούμαι:</b>	
	Μάλιστα σε πολύ μεγάλο βαθμό	3
	Σε αρκετά μεγάλο βαθμό	2
	Όχι σε τόσο μεγάλο βαθμό	1
	Καθόλου	0

<b>D.6</b>	<b>Προσμένω με χαρά διάφορα πράγματα:</b>	
	Τόσο όπως και στο παρελθόν	0
	Μάλλον λιγότερο απ' όσο συνήθιζα	1
	Σίγουρα λιγότερο απ' ότι συνήθιζα	2
	Καθόλου	3

<b>A.7</b>	<b>Αντιμετωπίζω αιφνίδια συναισθήματα πανικού:</b>	
	Πράγματι πολύ συχνά	3
	Αρκετά συχνά	2
	Όχι τόσο συχνά	1
	Καθόλου	0

<b>D.7</b>	<b>Μπορώ να απολαμβάνω ένα ενδιαφέρον βιβλίο ή ένα ραδιοφωνικό/τηλεοπτικό πρόγραμμα:</b>	
	Συχνά	0
	Μερικές φορές	1
	Όχι συχνά	2
	Πολύ σπάνια	3

**Παρακαλώ ελέγξτε ότι έχετε απαντήσει όλες τις ερωτήσεις.**

<b>A</b>		<b>D</b>		<b>T</b>	
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**Appendix 8.10. Hospital Anxiety and Depression Scale (HADS) (English version)****HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS)**

Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate is best.

Name: .....

Date: .....

<b>A.1</b>	<b>I feel tense or 'wound up':</b>	
	Most of the time	3
	A lot of the time	2
	From time to time, occasionally	1
	Not at all	0

<b>D.1</b>	<b>I still enjoy the things I used to enjoy:</b>	
	Definitely as much	0
	Not quite so much	1
	Only a little	2
	Hardly at all	3

<b>A.2</b>	<b>I get a sort of frightened feeling as if something awful is about to happen:</b>	
	Very definitely and quite badly	3
	Yes, but not too badly	2
	A little, but it doesn't worry me	1
	Not at all	0

<b>D.2</b>	<b>I can laugh and see the funny side of things:</b>	
	As much as I always could	0
	Not quite so much now	1
	Definitely not so much now	2
	Not at all	3

<b>A.3</b>	<b>Worrying thoughts go through my mind:</b>	
	A great deal of the time	3
	A lot of the time	2
	From time to time, but not too often	1
	Only occasionally	0

<b>D.3</b>	<b>I feel cheerful:</b>	
	Not at all	3
	Not often	2
	Sometimes	1
	Most of the time	0

<b>A.4</b>	<b>I can sit at ease and feel relaxed:</b>	
	Definitely	0
	Usually	1
	Not Often	2
	Not at all	3

<b>D.4</b>	<b>I feel as if I am slowed down:</b>	
	Nearly all the time	3
	Very often	2
	Sometimes	1
	Not at all	0

<b>A.5</b>	<b>I get a sort of frightened feeling like 'butterflies' in the stomach:</b>	
	Not at all	0
	Occasionally	1
	Quite Often	2
	Very Often	3

<b>D.5</b>	<b>I have lost interest in my appearance:</b>	
	Definitely	3
	I don't take as much care as I should	2
	I may not take quite as much care	1
	I take just as much care as ever	0



<b>A.6</b>	<b>I feel restless as I have to be on the move:</b>	
	Very much indeed	3
	Quite a lot	2
	Not very much	1
	Not at all	0

<b>D.6</b>	<b>I look forward with enjoyment to things:</b>	
	As much as I ever did	0
	Rather less than I used to	1
	Definitely less than I used to	2
	Hardly at all	3

<b>A.7</b>	<b>I get sudden feelings of panic:</b>	
	Very often indeed	3
	Quite often	2
	Not very often	1
	Not at all	0

<b>D.7</b>	<b>I can enjoy a good book or radio or TV program:</b>	
	Often	0
	Sometimes	1
	Not often	2
	Very seldom	3

Please check you have answered all the questions

<b>A</b>		<b>D</b>		<b>T</b>	
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**Appendix 8.11. UK PDS Brain Bank Criteria (adopted by NICE, 2006)**

Step 1. Diagnosis of a parkinsonian syndrome
<p>Bradykinesia and at least one of the following:</p> <ul style="list-style-type: none"> <li>• muscular rigidity</li> <li>• rest tremor (4–6 Hz)</li> <li>• postural instability unrelated to primary visual, cerebellar, vestibular or proprioceptive dysfunction.</li> </ul>
Step 2. Exclusion criteria for PD
<p>History of:</p> <ul style="list-style-type: none"> <li>• repeated strokes with stepwise progression</li> <li>• repeated head injury</li> <li>• antipsychotic or dopamine-depleting drugs</li> <li>• definite encephalitis and/or oculogyric crises on no drug treatment</li> <li>• more than one affected relative</li> <li>• sustained remission</li> <li>• negative response to large doses of levodopa (if malabsorption excluded)</li> <li>• strictly unilateral features after 3 years</li> <li>• other neurological features: supranuclear gaze palsy, cerebellar signs, early severe autonomic involvement, Babinski sign, early severe dementia with disturbances of language, memory or praxis</li> <li>• exposure to known neurotoxin</li> <li>• presence of cerebral tumour or communicating hydrocephalus on neuroimaging.</li> </ul>
Step 3. Supportive criteria for PD
<p>Three or more required for diagnosis of definite PD:</p> <ul style="list-style-type: none"> <li>• unilateral onset</li> <li>• excellent response to levodopa</li> <li>• rest tremor present <ul style="list-style-type: none"> <li>• severe levodopa-induced chorea</li> </ul> </li> <li>• progressive disorder</li> <li>• levodopa response for over 5 years</li> <li>• persistent asymmetry affecting the side of</li> <li>• clinical course of over 10 years.</li> </ul>

**Appendix 8.12.** Description of the Unified Parkinson's Disease Rating Scale (UPDRS).

The UPDRS is a combination of patient interview and physical examination. It consists of four parts and 42 items (Ebersbach et al., 2006). Specifically:

- Part I (mentation, behavior, and mood) includes four interview items.
- Part II (ADLs) includes 13 interview items.
- Part III (motor examination) includes 14 examination items.
- Part IV (complications of therapy) includes 11 items, a mixture of interview assessment plus yes/no responses based on rater judgment (Ebersbach et al., 2006).

The responses of the items are on a five-Likert scale rated from zero (normal) to four (severely affected); except the dichotomous items of part IV. Higher scores indicate greater impact of PD symptoms. The scores of all the subscales can be summed to a total UPDRS score. (Ebersbach et al., 2006). The (modified) H&Y scale and the SEADL scale are usually administered with the UPDRS (Sampaio et al., 2012). In the current study, the UPDRS was completed by the neurologist.

**Appendix 8.13. Unified Parkinson's Disease Rating Scale (UPDRS) (Greek version).****ΕΝΟΠΟΙΗΜΕΝΗ ΚΛΙΜΑΚΑ ΔΙΑΒΑΘΜΙΣΗΣ ΠΑΡΚΙΝΣΟΝ (UPDRS)****Όνομα:****Ημερομηνία:****A. Συμπεριφορά και διάθεση****I. Διανοητικές διαταραχές:**

0 = καμμία

1 = ήπια. Μερική δυσκολία

2 = μέτρια απώλεια μνήμης, μερικώς αποπροσανατολισμός και δυσκολία στην αντιμετώπιση δύσκολων προβλημάτων

3 = σοβαρή απώλεια μνήμης με αποπροσανατολισμό στον χρόνο και συχνά στον τόπο

4 = πολύ σοβαρή απώλεια μνήμης με πλήρη αποπροσανατολισμό. Ανίκανος να αντιμετωπίσει οποιοδήποτε

πρόβλημα. Έχει ανάγκη από προσωρινή φροντίδα. Δεν μπορεί να μείνει μόνος του.

**II. Διαταραχές σκέψης:**

0 = καμμία διαταραχή

1 = έντονα όνειρα

2 = παραισθήσεις

3 = παραισθήσεις αυτόματες. Μπορεί να ανταποκριθεί στις καθημερινές του δραστηριότητες

4 = παραισθήσεις επίμονες, αυταπάτες ή ψυχωτικές διαταραχές. Ανίκανος να φροντίζει τον εαυτό του.

**III. Κατάθλιψη:**

1 = περίοδοι θλίψης ή ενοχές περισσότερο από το κανονικό. Δεν παραμένει ποτέ για μέρες ή για βδομάδες

2 = συνεχής κατάθλιψη (για 1 εβδομάδα ή παραπάνω)

3 = συνεχής κατάθλιψη, η οποία συνοδεύεται από αϋπνίες, ανορεξία, χάσιμο βάρους, απώλεια ενδιαφέροντος

4 = συνεχής κατάθλιψη με συμπτώματα αυτοκαταστροφής.

**IV. Κίνητρα-Πρωτοβουλίες:**

0 = κανονικός

1 = λιγότερο κατανοητός από ότι συνήθως – περισσότερο παθητικός

2 = απώλεια πρωτοβουλίας σε ορισμένες δραστηριότητες

3 = απώλεια πρωτοβουλίας σε όλες τις καθημερινές δραστηριότητες

4 = απόσυρση - πλήρη απώλεια κινήτρων

**B. Δραστηριότητες της καθημερινής ζωής (ON και OFF φάση)****I. Ομιλία:**

0 = φυσιολογική

1 = ήπια επηρεασμένη - εύκολα κατανοητή

2 = λίγο επηρεασμένη. Μερικές φορές ζητείται από τον ασθενή να επαναλάβει τα λεγόμενά του

3 = σοβαρά επηρεασμένη ομιλία. Συχνά ζητείται από τον ασθενή να επαναλάβει τα λεγόμενά του

4 = δεν είναι κατανοητός ο λόγος του.

II. Σιελόρροια:

0 = καθόλου

1 = μικρή σιελόρροια, αλλά καθοριστική συγκέντρωση σιέλων στο στόμα. Μπορεί να έχει νυχτερινή σιελόρροια.

2 = μικρή σιελόρροια - μέτρια συγκέντρωση σιέλου στο στόμα

3 = σιελόρροια - αρκετή συγκέντρωση σιέλου στο στόμα

4 = πολύ σιελόρροια – απαιτείται η χρησιμοποίηση χαρτομάντιλου.

III. Κατάποση:

0 = φυσιολογική

1 = σπάνια πνιγμός

2 = περιστασιακά πνιγμός

3 = απαιτείται μαλακό φαγητό

4 = απαιτείται οισοφαγικός σωλήνας.

IV. Γραφή:

0 = φυσιολογική

1 = λίγο αργά. Όλες οι λέξεις δεν είναι αναγνώσιμες

2 = σχετικά αργά. Όλες οι λέξεις δεν είναι αναγνώσιμες

3 = σοβαρά επηρεασμένη η γραφή. Δεν είναι όλες οι λέξεις αναγνώσιμες

4 = η πλειοψηφία των λέξεων δεν είναι αναγνώσιμες.

V. Κόψιμο φαγητού:

0 = φυσιολογικά

1 = λίγο αργά, αλλά δεν χρειάζεται βοήθεια

2 = μπορεί να κόψει τα περισσότερα φαγητά αν και αδέξια και αργά. Χρειάζεται λίγη βοήθεια

3 = το φαγητό πρέπει να κοπεί από κάποιον άλλον, αλλά μπορεί ακόμα να φάει μόνος του αργά

4 = χρειάζεται κάποιον να τον ταΐσει.

VI. Ντύσιμο:

0 = κανονικό

1 = κάπως αργά, αλλά δεν χρειάζεται βοήθεια

2 = περιστασιακά χρειάζεται βοήθεια για το κούμπωμα, να βάλει το χέρι του στα μανίκια

3 = απαιτείται βοήθεια, αλλά μπορεί ακόμα να κάνει κάποια πράγματα μόνος του

4 = ανίσχυρος.

VII. Υγιεινή:

0 = φυσιολογική

1 = κάπως αργά, αλλά δεν χρειάζεται βοήθεια

2 = χρειάζεται βοήθεια για να κάνει ντους ή μπάνιο

3 = χρειάζεται βοήθεια για να πλυθεί, να πλύνει τα δόντια του, να φτιάξει τα μαλλιά του, να πάει στο μπάνιο

4 = είναι απαραίτητος ουροκαθετήρας ή άλλη μηχανική βοήθεια.

VIII. Γύρισμα στο κρεβάτι και αλλαγή σεντονιών:

0 = φυσιολογικός

1 = κάπως αργά και αδέξια, αλλά δεν χρειάζεται βοήθεια

2 = μπορεί να γυρίσει στο κρεβάτι ή να αλλάξει τα σεντόνια, αλλά με μεγάλη δυσκολία

3 = μπορεί να αρχίσει, αλλά να μην τελειώσει τις παραπάνω δραστηριότητες

4 = ανίσχυρος.

ΙΧ. Πτώση: (ανεξάρτητη από το φαινόμενο του freezing)

0 = καμμία

1 = σπάνιες πτώσεις

2 = περιστασιακές πτώσεις, λιγότερες από μια φορά την ημέρα

3 = πτώση κατά μέσο όρο μία την ημέρα

4 = πτώσεις περισσότερες από μία την ημέρα

Χ. Πάγωμα (freezing)

0 = καμμία

1 = σπάνια. Μπορεί να έχουν διστακτικότητα στην αρχή της κίνησης

2 = περιστασιακά όταν περπατά

3 = συχνά - περιστασιακές πτώσεις λόγω παγώματος

4 = συχνές πτώσεις από το πάγωμα

ΧΙ. Βάδιση:

0 = φυσιολογική

1 = ελάχιστη δυσκολία

2 = λίγη δυσκολία, αλλά χρειάζεται λίγη ή και καθόλου βοήθεια

3 = σοβαρές διαταραχές της βάδισης - απαιτείται βοήθεια

4 = δεν μπορεί να περπατήσει καθόλου ακόμα και με βοήθεια.

ΧΙΙ. Τρόμος:

0 = απών

1 = ελάχιστος και εμφανίζεται σπανίως

2 = λίγο - ενοχλητικός για τον ασθενή

3 = σοβαρός-παρεμποδίζει πολλές δραστηριότητες

4 = εγκατεστημένος - παρεμποδίζει σχεδόν όλες τις δραστηριότητες.

ΧΙΙΙ. Αισθητικές διαταραχές σχετικές με το Πάρκινσον:

0 = καμμία

1 = περιστασιακή αιμωδία, τσούξιμο ή ήπιο πόνο

2 = συνεχείς αιμωδίες, τσούξιμο, πόνο

3 = συχνός πόνος

4 = βασανιστικός πόνος.

**Γ. Κινητική αξιολόγηση**I. Ομιλία:

0 = φυσιολογική

1 = ελάχιστη διαταραχή της έκφρασης, άρθρωσης ή και φωνής

2 = μετρίως επηρεασμένη, μονότονη, ασαφής, αλλά κατανοητή

3 = αρκετά επηρεασμένη - δύσκολη στην κατανόηση

4 = ακατανόητη.

II. Έκφραση προσώπου:

0 = φυσιολογική

1 = ελάχιστη διαταραχή

2 = φανερή διαταραχή της έκφρασης του προσώπου

3 = μεγάλη δυστονία

4 = ανέκφραστο προσωπείο.

III. Τρόμος ηρεμίας:

0 = απών

1 = ελάχιστα και με πολύ μικρή συχνότητα εμφάνισης

2 = μικρή σε ένταση και διάρκεια ή μέση ένταση, αλλά μόνο μικρή συχνότητα

3 = μέση ένταση και συχνότητα εμφάνισης τις περισσότερες ώρες της ημέρας

4 = πολύ μεγάλης έντασης και εμφανίζεται τις περισσότερες ώρες της ημέρας.

IV. Τρόμος στα χέρια κατά την ηρεμία και την κίνηση:

0 = απών

1 = ελάχιστος – παρουσιάζεται κατά την κίνηση

2 = μικρής έντασης – εμφανίζεται μόνο στην κίνηση

3 = μικρής έντασης – εμφανίζεται και στην κίνηση και στην ηρεμία

4 = μεγάλης έντασης – επηρεάζει την αυτοεξυπηρέτηση

V. Ακαμψία:

0 = απουσία

1 = ελάχιστη ή ανεκτική

2 = μικρού προς μέσου βαθμού

3 = εγκατεστημένα, αλλά η ολοκλήρωση της τροχιάς επιτυγχάνεται εύκολα

4 = μεγάλου βαθμού – η τροχιά κίνησης επιτυγχάνεται με δυσκολία.

VI. Κίνηση δακτύλων: (ο ασθενής προσπαθεί να ακουμπήσει με τον αντίχειρα του τα υπόλοιπα δάκτυλα)

0 = φυσιολογική

1 = μικρή επιβάρυνση ή και μικρή ένταση της κίνησης

2 = μέση διαταραχή – καθοριστική και πρόωρη κόπωση

3 = μεγάλη διαταραχή – διστακτικότητα στην έναρξη της κίνησης ή της σύλληψης

4 = μόλις που μπορεί να ακουμπήσει τα υπόλοιπα δάκτυλα.

VII. Κινήσεις της άκρας χείρας: (ο ασθενής προσπαθεί να ανοίξει και να κλείσει τα χέρια του με μεγάλη ταχύτητα)

0 = φυσιολογική

1 = μικρή επιβάρυνση ή και μικρή ένταση της κίνησης

2 = μέση διαταραχή – καθοριστική και πρόωρη κόπωση

3 = μεγάλη διαταραχή – διστακτικότητα στην έναρξη της κίνησης ή της σύλληψης

4 = μόλις που μπορεί να ακουμπήσει τα υπόλοιπα δάκτυλα.

VIII. Γρήγορη εναλλαγή των κινήσεων των χεριών: (πρηνισμός – υπτιασμός και των δύο χεριών μαζί)

0 = φυσιολογική

1 = μικρή επιβάρυνση ή και μικρή ένταση της κίνησης

2 = μέση διαταραχή – καθοριστική και πρόωρη κόπωση

3 = μεγάλη διαταραχή – διστακτικότητα στην έναρξη της κίνησης ή της σύλληψης

4 = μόλις που μπορεί να ακουμπήσει τα υπόλοιπα δάκτυλα.

IX. Ελαστικότητα – Ευκινησία κάτω άκρων: (ο ασθενής πατά την πτέρνα στο έδαφος με γρήγορη κίνηση ακολουθώντας μετά ολόκληρο το πέλμα)

0 = φυσιολογική

1 = μικρή επιβάρυνση ή και μικρή ένταση της κίνησης

2 = μέση διαταραχή – καθοριστική και πρόωρη κόπωση

3 = μεγάλη διαταραχή – διστακτικότητα στην έναρξη της κίνησης ή της σύλληψης

4 = μόλις που μπορεί να ακουμπήσει τα υπόλοιπα δάκτυλα.

X. Να σηκωθεί από την καρέκλα:

0 = φυσιολογικό

1 = αργά ή μπορεί να χρειαστεί περισσότερες από μία προσπάθειες

2 = σηκώνεται χρησιμοποιώντας τα χέρια του

3 = έχει την τάση να ξαναπέσει πίσω και μπορεί να χρειαστεί περισσότερες από μία προσπάθειες. Μπορεί, όμως να σηκωθεί και χωρίς βοήθεια

4 = ανίκανος να σηκωθεί χωρίς βοήθεια.

XI. Στάση:

0 = φυσιολογική

1 = δεν είναι εντελώς κάθετη με το έδαφος, μπορεί να είναι φυσιολογική για ηλικιωμένα άτομα

2 = μη φυσιολογική στάση – μπορεί να γέρνει προς την μία πλευρά

3 = μεγάλη διαταραχή της στάσης με κύφωση

4 = μεγάλη κάμψη της Σ.Σ. με έντονες διαταραχές της στάσης.

XII. Βάδιση:

0 = φυσιολογική

1 = περπατά αργά – πραγματοποιείται η εναλλαγή του βήματος με μικρό δρασκέλισμα

2 = περπατά με δυσκολία, αλλά απαιτείται μικρή ή ελάχιστη βοήθεια

3 = μεγάλη διαταραχή της βάδισης, απαιτείται βοήθεια

4 = δεν μπορεί να περπατήσει ακόμα και με βοήθεια.

XIII. Ισορροπία: (με τα μάτια ανοιχτά)

0 = φυσιολογική

1 = μερική έλλειψη ισορροπίας σε δοκιμασία διαταραχής της με τάση επανάκτησής της

2 = σε διαταραχή της ισορροπίας από τον εξεταστή υπάρχει κίνδυνος πτώσης εάν ο τελευταίος δεν τον κρατήσει

3 = μεγάλη αστάθεια – έχει την τάση να χάνει την ισορροπία του χωρίς εξωτερική διαταραχή

4 = δεν μπορεί να σταθεί όρθιος χωρίς βοήθεια.

XIV. Βραδυκίνησια και υποκίνησια:

0 = καμιά

1 = ελάχιστη βραδύτητα που δίνει στην μετακίνηση ένα σκόπιμο χαρακτήρα. Μπορεί να είναι φυσιολογικό για ορισμένους ανθρώπους. Ενδεχόμενο μειωμένο εύρος

2 = μικρού βαθμού βραδυκίνησια και έλλειψη της κίνησης, η οποία είναι διαταραγμένη. Μειωμένο εύρος κίνησης

3 = μεσαίου βαθμού βραδυκίνησια, έλλειψη ή μικρού εύρους κίνησης

4 = χαρακτηριστική βραδύτητα, έλλειψη ή μικρού εύρους κίνησης.

**Δ. Επιπλοκές κατά την διάρκεια της θεραπείας (τη περασμένη εβδομάδα)**I. Δυσκίνησια:

α) Διάρκεια: σε τι ποσοστό της ημέρας εμφανίζεται η δυσκίνησια (ιστορικό ασθενή)

0 = καθόλου

1 = 1 – 25% την ημέρα

2 = 26 – 50% την ημέρα

3 = 51 – 75% την ημέρα

4 = 76 – 100% την ημέρα



b) Ανικανότητα λόγω δυσκαμψίας (ιστορικό ασθενή και εξέταση)

0 = καμμιά

1 = μικρή

2 = μεσαία

3 = μεγάλη

4 = τέλεια

c) Επίπονη δυσκινησία:

0 = καθόλου

1 = πολύ μικρή

2 = μεσαία

3 = πολύ μικρή

4 = εγκατεστημένη

d) Παρουσία δυστονίας νωρίς το πρωί

0 = όχι

1 = ναι

## II. Κλινικές διακυμάνσεις:

a) Είναι το τέλος (OFF) της περιόδου προβλεπόμενο;

0 = όχι

1 = ναι

b) Είναι το τέλος (OFF) της περιόδου απρόβλεπτο;

0 = όχι

1 = ναι

c) Το τέλος (OFF) των συμπτωμάτων έρχεται ξαφνικά; Μέσα σε λίγα δευτερόλεπτα;

0 = όχι

1 = ναι

d) Ποιο ποσοστό της ημέρας (όταν ο ασθενής ξυπνά) είναι ο ασθενής χωρίς (OFF) συμπτώματα κατά μέσο όρο;

0= κανένα

1= 1 – 25% της ημέρας

2= 26 – 50% της ημέρας

3= 51 – 75% της ημέρας

4= 76 – 100% της ημέρας

## III. Άλλες κλινικές επιπλοκές

Ο ασθενής έχει ανορεξία, ναυτία, εμετό:

0 = όχι

1 = ναι

Υπάρχουν επιπλοκές ύπνου, όπως αϋπνίες ή υπνηλία:

0 = όχι

1 = ναι

Έχει ο ασθενής ορθοστατική υπόταση;

0 = όχι

1 = ναι

**Appendix 8.14. Unified Parkinson's Disease Rating Scale (UPDRS) (English version).**

## **UNIFIED PARKINSON'S DISEASE RATING SCALE**

**Name:**

**Date:**

### **A. MENTATION, BEHAVIOR AND MOOD**

#### **I. Intellectual Impairment**

0 = None.

1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.

2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.

3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.

4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.

#### **II. Thought Disorder (Due to dementia or drug intoxication)**

0 = None.

1 = Vivid dreaming.

2 = "Benign" hallucinations with insight retained.

3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.

4 = Persistent hallucinations, delusions, or florid psychosis. Not able to care for self.

#### **III. Depression**

0 = None.

1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.

2 = Sustained depression (1 week or more).

3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).

4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

#### **IV. Motivation/Initiative**

0 = Normal.

1 = Less assertive than usual; more passive.

2 = Loss of initiative or disinterest in elective (nonroutine) activities.

3 = Loss of initiative or disinterest in day to day (routine) activities.

4 = Withdrawn, complete loss of motivation.

**B. ACTIVITIES OF DAILY LIVING (for both “on” and “off”)**

**I. Speech**

0 = Normal.

1 = Mildly affected. No difficulty being understood.

2 = Moderately affected. Sometimes asked to repeat statements.

3 = Severely affected. Frequently asked to repeat statements.

4 = Unintelligible most of the time.

**II. Salivation**

0 = Normal.

1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.

2 = Moderately excessive saliva; may have minimal drooling.

3 = Marked excess of saliva with some drooling.

4 = Marked drooling, requires constant tissue or handkerchief.

**III. Swallowing**

0 = Normal.

1 = Rare choking.

2 = Occasional choking.

3 = Requires soft food.

4 = Requires NG tube or gastrotomy feeding.

**IV. Handwriting**

0 = Normal.

1 = Slightly slow or small.

2 = Moderately slow or small; all words are legible.

3 = Severely affected; not all words are legible.

4 = The majority of words are not legible.

**V. Cutting food and handling utensils**

0 = Normal.

1 = Somewhat slow and clumsy, but no help needed.

2 = Can cut most foods, although clumsy and slow; some help needed.

3 = Food must be cut by someone, but can still feed slowly.

4 = Needs to be fed.

VI. Dressing

0 = Normal.

1 = Somewhat slow, but no help needed.

2 = Occasional assistance with buttoning, getting arms in sleeves.

3 = Considerable help required, but can do some things alone.

4 = Helpless.

VII. Hygiene

0 = Normal.

1 = Somewhat slow, but no help needed.

2 = Needs help to shower or bathe; or very slow in hygienic care.

3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.

4 = Foley catheter or other mechanical aids.

VIII. Turning in bed and adjusting bed clothes

0 = Normal.

1 = Somewhat slow and clumsy, but no help needed.

2 = Can turn alone or adjust sheets, but with great difficulty.

3 = Can initiate, but not turn or adjust sheets alone.

4 = Helpless.

IX. Falling (unrelated to freezing)

0 = None.

1 = Rare falling.

2 = Occasionally falls, less than once per day.

3 = Falls an average of once daily.

4 = Falls more than once daily.

X. Freezing when walking

0 = None.

1 = Rare freezing when walking; may have start hesitation.

2 = Occasional freezing when walking.

3 = Frequent freezing. Occasionally falls from freezing.

4 = Frequent falls from freezing.

XI. Walking

0 = Normal.

1 = Mild difficulty. May not swing arms or may tend to drag leg.

2 = Moderate difficulty, but requires little or no assistance.

3 = Severe disturbance of walking, requiring assistance.

4 = Cannot walk at all, even with assistance.

XII. Tremor (Symptomatic complaint of tremor in any part of body)

0 = Absent.

1 = Slight and infrequently present.

2 = Moderate; bothersome to patient.

3 = Severe; interferes with many activities.

4 = Marked; interferes with most activities.

XIII. Sensory complaints related to parkinsonism

0 = None.

1 = Occasionally has numbness, tingling, or mild aching.

2 = Frequently has numbness, tingling, or aching; not distressing.

3 = Frequent painful sensations.

4 = Excruciating pain.

**C. MOTOR EXAMINATION**

I. Speech

0 = Normal.

1 = Slight loss of expression, diction and/or volume.

2 = Monotone, slurred but understandable; moderately impaired.

3 = Marked impairment, difficult to understand.

4 = Unintelligible.

II. Facial Expression

0 = Normal.

1 = Minimal hypomimia, could be normal "Poker Face".

2 = Slight but definitely abnormal diminution of facial expression.

3 = Moderate hypomimia; lips parted some of the time.

4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

III. Tremor at rest (head, upper and lower extremities)

0 = Absent.

1 = Slight and infrequently present.

2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.

3 = Moderate in amplitude and present most of the time.

4 = Marked in amplitude and present most of the time.

IV. Action or Postural Tremor of hands

0 = Absent.

1 = Slight; present with action.

2 = Moderate in amplitude, present with action.

3 = Moderate in amplitude with posture holding as well as action.

4 = Marked in amplitude; interferes with feeding.

V. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cog wheeling to be ignored.)

0 = Absent.

1 = Slight or detectable only when activated by mirror or other movements.

2 = Mild to moderate.

3 = Marked, but full range of motion easily achieved.

4 = Severe, range of motion achieved with difficulty.

VI. Finger Taps (Patient taps thumb with index finger in rapid succession)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

VII. Hand Movements (Patient opens and closes hands in rapid succession)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

VIII. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

IX. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

X. Arising from chair (Patient attempts to rise from a straight backed chair, with arms folded across chest)

0 = Normal.

1 = Slow; or may need more than one attempt.

2 = Pushes self-up from arms of seat.

3 = Tends to fall back and may have to try more than one time, but can get up without help.

4 = Unable to arise without help.

XI. Posture

0 = Normal erect.

1 = Not quite erect, slightly stooped posture; could be normal for older person.

2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.

3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.

4 = Marked flexion with extreme abnormality of posture.

XII. Gait

0 = Normal.

1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.

2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.

3 = Severe disturbance of gait, requiring assistance.



4 = Cannot walk at all, even with assistance.

XIII. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared)

0 = Normal.

1 = Retropulsion, but recovers unaided.

2 = Absence of postural response; would fall if not caught by examiner.

3 = Very unstable, tends to lose balance spontaneously.

4 = Unable to stand without assistance.

XIV. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased arm swing, small amplitude, and poverty of movement in general)

0 = None.

1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.

2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.

3 = Moderate slowness, poverty or small amplitude of movement.

4 = Marked slowness, poverty or small amplitude of movement.

**D. COMPLICATIONS OF THERAPY (In the past week)**

DYSKINESIAS

I. Duration: What proportion of the waking day are dyskinesias present?

0 = None.

1 = 1-25% of day.

2 = 26-50% of day.

3 = 51-75% of day.

4 = 76-100% of day.

II. Disability: How disabling are the dyskinesias?

0 = Not disabling.

1 = Mildly disabling.

2 = Moderately disabling.

3 = Severely disabling.

4 = Completely disabled.

III. Painful Dyskinesias: How painful are the dyskinesias?

0 = No painful dyskinesias.

1 = Slight.

2 = Moderate.

3 = Severe.

4 = Marked.

IV. Presence of Early Morning Dystonia

0 = No

1 = Yes

CLINICAL FLUCTUATIONS

I. Are "off" periods predictable?

0 = No

1 = Yes

II. Are "off" periods unpredictable?

0 = No

1 = Yes

III. Do "off" periods come on suddenly, within a few seconds?

0 = No

1 = Yes

IV. What proportion of the waking day is the patient "off" on average?

0 = None

1 = 1-25% of day.

2 = 26-50% of day.

3 = 51-75% of day.

4 = 76-100% of day.

OTHER COMPLICATIONS

I. Does the patient have anorexia, nausea, or vomiting?

0 = No

1 = Yes

II. Any sleep disturbances, such as insomnia or hypersomnolence?

0 = No

1 = Yes

III. Does the patient have symptomatic orthostasis?

(Record the patient's blood pressure, height and weight on the scoring form)

0 = No

1 = Yes

**Appendix 8.15.** Description of the Modified Hoehn and Yahr (H&Y) Scale.

The Modified H&Y scale is a more recent version of the original H&Y scale with the addition of stages 1.5 and 2.5. Thus, it has seven stages instead of five. It is a “rate-as-you-see” approach, based on observation and examination of functional mobility (Sampaio et al., 2012). In the present project, the Modified H&Y Scale was completed by the neurologist.

**Appendix 8.16. Modified Hoehn and Yahr (H&Y) Scale (Greek version).****ΤΡΟΠΟΠΟΙΗΜΕΝΗ ΚΛΙΜΑΚΑ ΗΟΕΗΝ & ΥΑΗΡ****Όνομα:****Ημερομηνία:**

<b>ΣΤΑΔΙΟ</b>	<b>ΣΥΜΠΤΩΜΑΤΑ</b>	<b>ΕΠΙΛΟΓΗ (X)</b>
Στάδιο 0	Κανένα εμφανές σύμπτωμα της νόσου του Πάρκινσον.	
Στάδιο 1	Μονόπλευρη πάθηση: Εμφάνιση συμπτωμάτων μόνο στην μία πλευρά του σώματος.	
Στάδιο 1,5	Μονόπλευρη πάθηση και συμμετοχή κορμού	
Στάδιο 2	Μονόπλευρη πάθηση: Εμφάνιση συμπτωμάτων και στις δύο πλευρές του σώματος αλλά καμιά διαταραχή στην ισορροπία και καμιά δυσκολία στην βάδιση.	
Στάδιο 2,5	Μονόπλευρη πάθηση με ανάκτηση στο pull test.	
Στάδιο 3	Ήπια προς μεσαίου βαθμού αμφοτερόπλευρη πάθηση: Εμφάνιση ήπιας και μέτριας βαρύτητας συμπτωμάτων και στις δύο πλευρές του σώματος, κάποια διαταραχή στην ισορροπία και ελάχιστη δυσκολία στην βάδιση. Ο ασθενής είναι πλήρως ανεξάρτητος.	
Στάδιο 4	Εμφάνιση σοβαρών συμπτωμάτων και στις δύο πλευρές του σώματος και μέτρια δυσκολία στην βάδιση. Ο ασθενής είναι ικανός να σταθεί και να βαδίσει χωρίς βοήθεια.	
Στάδιο 5	Εμφάνιση συμπτωμάτων και στις δύο πλευρές του σώματος και ανικανότητα βάδισης. Ο ασθενής είναι καθηλωμένος στην αναπηρική καρέκλα και μπορεί να σηκωθεί μόνο με την βοήθεια άλλων.	

**Appendix 8.17. Modified Hoehn and Yahr (H&Y) Scale (English version).****MODIFIED HOEHN AND YAHR STAGING****Name:****Date:**

STAGE	SYMPTOMS	CHOICE (X)
0	No signs of disease.	
1	Unilateral disease.	
1.5	Unilateral plus axial involvement.	
2	Bilateral disease, without impairment of balance.	
2.5	Mild bilateral disease, with recovery on pull test.	
3	Mild to moderate bilateral disease; some postural instability; physically independent.	
4	Severe disability; still able to walk or stand unassisted.	
5	Severe disability; still able to walk or stand unassisted.	

**Appendix 8.18.** Description of the Schwab and England Activities of Daily Living (SEADL) Scale.

The SEADL includes 11 stages, and rates the ability of PD patients to perform ADLs from 100% (essential normal) to 0% (vegetative) (McRae et al., 2002). In the current study, the scale was shown to the individuals to select the rating that most accurately described their level of functional independence.

## Appendix 8.19. Schwab and England Activities of Daily Living (SEADL) Scale (Greek version)

## ΚΛΙΜΑΚΑ ΚΑΘΗΜΕΡΙΝΩΝ ΔΡΑΣΤΗΡΙΟΤΗΤΩΝ SEADL

Όνομα:

Ημερομηνία:

ΣΤΑΔΙΟ		ΕΠΙΛΟΓΗ
100%	Εντελώς ανεξάρτητος. Είναι σε θέση να κάνει όλες τις δουλειές χωρίς καθυστέρηση, δυσκολία ή βλάβη. Ουσιαστικά φυσιολογικός. Δεν γνωρίζει καμία δυσκολία	
90%	Εντελώς ανεξάρτητος. Είναι σε θέση να κάνει όλες τις δουλειές με κάποιο βαθμό βραδύτητας, δυσκολίας και δυσλειτουργίας. Μπορεί να πάρει δύο φορές περισσότερο χρόνο. Ξεκινά να υπάρχει δυσκολία.	
80%	Πλήρως ανεξάρτητος στις περισσότερες δουλειές. Διαρκεί δύο φορές περισσότερο χρόνο. Υπάρχει επίγνωση της δυσκολίας και της βραδύτητας.	
70%	Όχι εντελώς ανεξάρτητος. Περισσότερες δυσκολίες με κάποιες δουλειές. Τρεις έως τέσσερις φορές περισσότερος χρόνος. Μπορεί να κάνει δουλειές τις περισσότερες ώρες της ημέρας.	
60%	Κάποια εξάρτηση. Μπορεί να κάνει τις περισσότερες δουλειές, αλλά εξαιρετικά αργά και με μεγάλη προσπάθεια. Σφάλματα σε μερικές, ενώ άλλες είναι αδύνατες.	
50%	Περισσότερη εξάρτηση. Δυσκολία με τα πάντα.	
40%	Μεγάλη εξάρτηση. Χρειάζεται βοήθεια στις περισσότερες δουλειές.	
30%	Με μεγάλη προσπάθεια, γίνονται κάποιες δουλειές ή ξεκινούν να γίνονται. Χρειάζεται μεγάλη βοήθεια.	
20%	Τίποτα μόνος. Σπάνια κάνει κάποια δουλειά μόνος.	
10%	Εντελώς εξαρτημένος και ανήμπορος.	
0%	Κλινικής. Ζωτικές λειτουργίες είναι σε καταστολή.	



**Appendix 8.20. Schwab and England Activities of Daily Living (SEADL) Scale (English version).**
**SCHWAB AND ENGLAND ACTIVITIES OF DAILY LIVING SCALE**
**Name:**
**Date:**

STAGE		CHOICE
100%	Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially normal. Unaware of any difficulty.	
90%	Completely independent. Able to do all chores with some degree of slowness, difficulty and impairment. Might take twice as long. Beginning to be aware of difficulty.	
80%	Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.	
70%	Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores.	
60%	Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible.	
50%	More dependent. Help with half, slower, etc. Difficulty with everything.	
40%	Very dependent. Can assist with all chores, but few alone.	
30%	With effort, now and then does a few chores alone or begins alone. Much help needed.	
20%	Nothing alone. Can be a slight help with some chores. Severe invalid.	
10%	Totally dependent, helpless. Complete invalid.	
0%	Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Bedridden.	

**Appendix 8.21.** Description of the Mini Mental State Examination (MMSE).

The MMSE consists of 11 tasks, grouped into seven cognitive domains: orientation to time, orientation to place, registration of three words, attention and calculation, recall of three words, language, and visual construction. The maximum score is 30 points. High scores indicate good performance, whereas 24 points and below indicate an abnormal result (cognitive impairment). Dementia is assumed for less than 20 points. (Sampaio et al., 2012). In the current project, the MMSE was completed by the assistant physiotherapist.

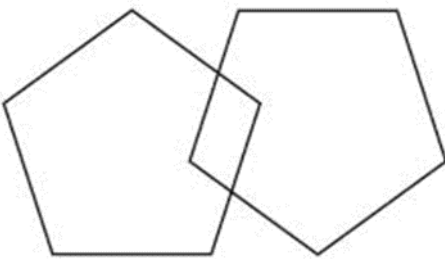
## Appendix 8.22. Mini Mental State Examination (MMSE) (Greek version).

**ΠΡΟΚΑΘΟΡΙΣΜΕΝΟ ΣΥΝΤΟΜΟ ΤΕΣΤ ΜΝΗΜΗΣ (MMSE)**

Όνομα:

Ημερομηνία:

A/A	ΕΡΩΤΗΣΗ	ΧΡΟΝΟΣ ΑΠΑΝΤΗΣΗΣ	ΒΑΘΜΟΛΟΓΙΑ
<b>ΠΡΟΣΑΝΑΤΟΛΙΣΜΟΣ</b>			
01Α	Τι έτος έχουμε;	10 δευτερόλεπτα	/1
01Β	Ποια εποχή;	10 δευτερόλεπτα	/1
01Γ	Τι μήνα;	10 δευτερόλεπτα	/1
01Δ	Πόσο του μήνα έχουμε;	10 δευτερόλεπτα	/1
01Ε	Ποια μέρα της εβδομάδας;	10 δευτερόλεπτα	/1
01ΣΤ	Σε ποια χώρα βρισκόμαστε;	10 δευτερόλεπτα	/1
01Ζ	Σε ποια πόλη;	10 δευτερόλεπτα	/1
01Η	Σε ποια περιοχή ή διεύθυνση;	10 δευτερόλεπτα	/1
01Θ	Σε πιο μέρος (όνομα κτηρίου) βρίσκεστε αυτή τη στιγμή;	10 δευτερόλεπτα	/1
01Ι	Σε ποιο όροφο;	10 δευτερόλεπτα	/1
<b>ΚΑΤΑΓΡΑΦΗ</b>			
02	Θα σας πω 3 λέξεις που θέλω να επαναλάβετε μετά από μένα και να τις θυμάστε όταν τις ξαναρωτήσω: λεμόνι-κλειδί-μολύβι	20 δευτερόλεπτα	/3
<b>ΣΥΓΚΕΝΤΡΩΣΗ/ΔΥΝΑΤΟΤΗΤΑ ΑΡΙΘΜΗΤΙΚΩΝ ΠΡΑΞΕΩΝ</b>			
03	Αφαιρέστε από το 100 διαδοχικά 7 μονάδες κάθε φορά / Εναλλακτικά: Γράψτε τη λέξη «πόρτα» ανάποδα (απάντηση: 93-86-79-72-65 / ΑΤΡΟΠ)	30 δευτερόλεπτα	/5

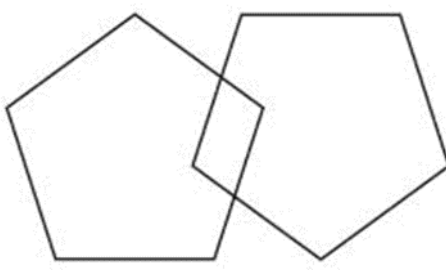
ΑΝΑΚΛΗΣΗ			
04	Επαναλάβετε παρακαλώ τις 3 λέξεις που σας είχα ζητήσει προηγουμένως (απάντηση: λεμόνι-κλειδί-μολύβι)	10 δευτερόλεπτα	/3
ΚΑΤΟΝΟΜΑΣΙΑ			
05	Δείχνουμε στον ασθενή 2 αντικείμενα και ζητούμε να τα κατονομάσει – τι είναι αυτό; (π.χ. ρολόι, μολύβι)	20 δευτερόλεπτα	/2
ΕΠΑΝΑΛΗΨΗ			
06	Ζητήστε από τον ασθενή να επαναλάβει μετά από σας: «Όχι αν και ή αλλά»	10 δευτερόλεπτα	/1
ΕΚΤΕΛΕΣΗ ΕΝΤΟΛΗΣ 3 ΣΤΑΔΙΩΝ			
07	Ρωτήστε τον ασθενή αν είναι δεξιόχειρας ή αριστερόχειρας. Δώστε στον ασθενή ένα λευκό φύλλο χαρτί και πείτε του: Α) Πάρτε το χαρτί στο δεξί/αριστερό σας χέρι, Β) Διπλώστε το στη μέση, Γ) Αφήστε το στο πάτωμα	30 δευτερόλεπτα	/3
ΑΝΤΙΔΡΑΣΗ			
08	Δείξτε στον ασθενή ένα χαρτί που να γράφει: «Κλείστε τα μάτια σας». Πείτε του να κάνει ό,τι γράφει το χαρτί που του δείχνετε. Αν ο ασθενής το διαβάσει και δεν κλείσει τα μάτια του, επαναλάβετε 3 φορές.	10 δευτερόλεπτα	/1
ΑΥΤΟΜΑΤΗ ΓΡΑΦΗ			
09	Δώστε στον ασθενή χαρτί και μολύβι και πείτε του να γράψει μια ολοκληρωμένη πρόταση (πρέπει να περιέχει υποκείμενο – ρήμα και η πρόταση να βγάζει νόημα, αγνοήστε τα ορθογραφικά λάθη)	30 δευτερόλεπτα	/1
ΑΝΤΙΓΡΑΦΗ			
10	Ζητήστε από τον ασθενή να αντιγράψει ένα σχήμα δύο τεμνόμενων πενταγώνων. 	60 δευτερόλεπτα	/1

	Επιτρέψτε πολλές προσπάθειες. Περιμένετε μέχρι να τελειώσει.		
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**ΣΥΝΟΛΙΚΟ ΑΘΡΟΙΣΜΑ MMSE:** \_\_\_\_\_

**Appendix 8.23. Mini Mental State Examination (MMSE) (English version).****MINI MENTAL STATE EXAMINATION (MMSE)****Name:****Date:**

No	QUESTION	TIME ALLOWED	SCORE
<b>ORIENTATION TO TIME</b>			
01A	What year is this?	10 seconds	/1
01B	Which season is this?	10 seconds	/1
01C	What month is this?	10 seconds	/1
01D	What is today's date?	10 seconds	/1
01E	What day of the week is this?	10 seconds	/1
<b>ORIENTATION TO PLACE</b>			
01F	What country are we in?	10 seconds	/1
01G	What province are we in?	10 seconds	/1
01H	What city/town are we in?	10 seconds	/1
01I	What is the name of this building?	10 seconds	/1
01J	What floor are we on?	10 seconds	/1
<b>REGISTRATION</b>			
02	SAY: I am going to name three objects. When I am finished, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes. (Say the following words slowly at 1-second intervals - ball/ car/ man)	20 seconds	/3
<b>ATTENTION &amp; CALCULATION</b>			
03	Spell the word WORLD. Now spell it backwards.	30 seconds	/5
<b>RECALL</b>			
04	Now what were the three objects I asked you to remember?	10 seconds	/3
<b>LANGUAGE</b>			
05	SHOW wristwatch. ASK: What is this called? SHOW pencil. ASK: What is this called?	20 seconds	/2

06	SAY: I would like you to repeat this phrase after me: No ifs, ands or buts.	10 seconds	/1
07	ASK the person if he is right or left-handed. Take a piece of paper and hold it up in front of the person. SAY: Take this paper in your right/left hand (whichever is non-dominant), fold the paper in half once with both hands and put the paper down on the floor . Score 1 point for each instruction executed correctly. Takes paper correctly in hand Folds it in half Puts it on the floor	30 seconds	 /1 /1 /1
08	SAY: Read the words on the page and then do what it says. Then hand the person the sheet with CLOSE YOUR EYES on it. If the subject reads and does not close their eyes, repeat up to three times. Score only if subject closes eyes	10 seconds	/1
09	HAND the person a pencil and paper. SAY: Write any complete sentence on that piece of paper. (Note: The sentence must make sense. Ignore spelling errors)	30 seconds	/1
<b>VISUAL CONSTRUCTION</b>			
10	PLACE design, eraser and pencil in front of the person. SAY: Copy this design please.    Allow multiple tries. Wait until person is finished and hands it back. Score only for correctly copied diagram with a 4-sided figure between two 5-sided figures.	60 seconds	/1

**TOTAL TEST SCORE:** \_\_\_\_\_

## Appendix 8.24. General Health Questionnaire (GHQ) (Greek version).

## ΓΕΝΙΚΟ ΕΡΩΤΗΜΑΤΟΛΟΓΙΟ (GHQ)

(Α) ΓΕΝΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ					
01	Όνομα				
02	Ημερομηνία		03	Κωδικός	
04	Δήμος		05	Τηλέφωνο	
06	Επάγγελμα	<input type="checkbox"/> συνταξιούχος <input type="checkbox"/> οικιακά <input type="checkbox"/> άνεργος <input type="checkbox"/> εργαζόμενος Αν είστε εργαζόμενος, συμπληρώστε το επάγγελμά σας:			
07	Οικογενειακή κατάσταση	<input type="checkbox"/> παντρεμένος <input type="checkbox"/> χωρισμένος <input type="checkbox"/> χήρος <input type="checkbox"/> ελεύθερος <input type="checkbox"/> διαζευγμένος <input type="checkbox"/> σε σχέση			
08	Ομιλούμενη γλώσσα	<input type="checkbox"/> ελληνικά <input type="checkbox"/> αγγλικά <input type="checkbox"/> άλλη: Ξέρετε να διαβάζετε και να γράφετε ελληνικά; <input type="checkbox"/> ναι <input type="checkbox"/> όχι			
09	Μπορείτε να παρακολουθήσετε το πρόγραμμα άσκησης (συχνότητα: 2 φορές τη βδομάδα, διάρκεια συνεδρίας: 1 ώρα, συνολική διάρκεια προγράμματος: 8 εβδομάδες, 3 αξιολογήσεις) <input type="checkbox"/> ναι <input type="checkbox"/> όχι				

(Β) ΣΩΜΑΤΟΜΕΤΡΙΚΑ ΧΑΡΑΚΤΗΡΙΣΤΙΚΑ					
01	Φύλο	<input type="checkbox"/> άνδρας <input type="checkbox"/> γυναίκα			
02	Ηλικία (σε έτη)		03	Ύψος (σε μέτρα)	
04	Βάρος (σε κιλά)		05	ΔΜΣ	
06	Εθνικότητα	<input type="checkbox"/> ελληνική <input type="checkbox"/> άλλη:			



(Γ) ΑΤΟΜΙΚΟ ΙΣΤΟΡΙΚΟ ΓΙΑ ΠΑΡΚΙΝΣΟΝ		
01	Πάθηση	<input type="checkbox"/> Πάρκινσον <input type="checkbox"/> εξωπυραμυδική συνδρομή <input type="checkbox"/> παρκινσονικό σύνδρομο
02	Τύπος Πάρκινσον	<input type="checkbox"/> ιδιοπαθής <input type="checkbox"/> δευτεροπαθής
03	Ιατρική διάγνωση	<input type="checkbox"/> ναι <input type="checkbox"/> όχι
04	Πόσο καιρό έχετε διαγνωστεί με Πάρκινσον;	
05	H&Y στάδιο	
06	Φάρμακα για Πάρκινσον	
07	Έχει αλλάξει η φαρμακευτική σας αγωγή της τελευταίες 4 εβδομάδες ή πρόκειται ν' αλλάξει σύντομα; <input type="checkbox"/> ναι <input type="checkbox"/> όχι <input type="checkbox"/> άλλο:	
08	Ποιες ώρες της ημέρας λειτουργεί καλύτερα η φαρμακευτική σας αγωγή για το Parkinson / Ποιες ώρες της ημέρας είστε καλύτερα κινητικά;	
09	Έχετε υποβληθεί σε χειρουργική επέμβαση (π.χ. εν τω βάθει ηλεκτρικός ερεθισμός / deep brain stimulation) λόγω του Πάρκινσον; <input type="checkbox"/> ναι <input type="checkbox"/> όχι <input type="checkbox"/> στο μέλλον (προσδιορίστε χρόνο: ..... )	
10	Λαμβάνετε κάποια μη φαρμακευτική αγωγή για το Πάρκινσον; <input type="checkbox"/> ναι <input type="checkbox"/> όχι  Αν απαντήσατε ναι, παρακαλώ προσδιορίστε: <input type="checkbox"/> φυσικοθεραπεία <input type="checkbox"/> λογοθεραπεία <input type="checkbox"/> ψυχολογική θεραπεία <input type="checkbox"/> διατροφή <input type="checkbox"/> άλλο: .....	

(Δ) ΥΠΟΛΟΙΠΟ ΑΤΟΜΙΚΟ ΙΑΤΡΙΚΟ ΙΣΤΟΡΙΚΟ		
01	Κάπνισμα	<input type="checkbox"/> όχι <input type="checkbox"/> συστηματικά <input type="checkbox"/> περιστασιακά <input type="checkbox"/> στο παρελθόν
02	Περπάτημα	<input type="checkbox"/> ανεξάρτητα <input type="checkbox"/> με βοηθητικό μέσο: Προσδιορίστε:

<b>03</b>	Βαθμολογία MMSE		
<b>04</b>	Καρδιολογική πάθηση	<input type="checkbox"/> στεφανιαία νόσος <input type="checkbox"/> στηθάγχη <input type="checkbox"/> έμφραγμα <input type="checkbox"/> υπέρταση <input type="checkbox"/> άλλο. Προσδιορίστε:	
<b>05</b>	Αναπνευστική πάθηση	<input type="checkbox"/> ΧΑΠ <input type="checkbox"/> άσθμα <input type="checkbox"/> άλλο. Προσδιορίστε :	
<b>06</b>	Νευρολογική πάθηση	<input type="checkbox"/> εγκεφαλικό επεισόδιο <input type="checkbox"/> άλλο:	
<b>07</b>	Μυοσκελετική πάθηση	<input type="checkbox"/> αυχενικό <input type="checkbox"/> οσφυαλγία <input type="checkbox"/> οστεοαρθρίτιδα <input type="checkbox"/> οστεοπόρωση <input type="checkbox"/> ρευματικά. Προσδιορίστε: <input type="checkbox"/> τραυματισμός. Προσδιορίστε: <input type="checkbox"/> άλλο. Προσδιορίστε:	
<b>08</b>	Άλλη πάθηση / άλλα προβλήματα	<input type="checkbox"/> διαβήτης (ινσουλοεξαρτώμενος) <input type="checkbox"/> ίλιγγος/ζαλάδες <input type="checkbox"/> χοληστερίνη <input type="checkbox"/> άλλο. Προσδιορίστε:	
<b>09</b>	Χειρουργική επέμβαση	<input type="checkbox"/> ναι <input type="checkbox"/> όχι Αν ναι, που και πότε:	
<b>10</b>	Σωματικός πόνος	<input type="checkbox"/> ναι <input type="checkbox"/> όχι Αν ναι, προσδιορίστε:	
<b>11</b>	Πρόβλημα ακοής /όρασης	<input type="checkbox"/> ναι <input type="checkbox"/> όχι Αν ναι, προσδιορίστε:	
<b>12</b>	Πτώση τους τελευταίους 2 μήνες	<input type="checkbox"/> ναι <input type="checkbox"/> όχι	
<b>13</b>	Κάνετε κάποιου είδους δίαιτα ή διατροφή; <input type="checkbox"/> ναι <input type="checkbox"/> όχι Αν ναι, για ποιο λόγο:		
<b>14</b>	Ψυχικά νοσήματα	<input type="checkbox"/> κατάθλιψη <input type="checkbox"/> αγχώδης διαταραχή <input type="checkbox"/> άλλο. Προσδιορίστε: Αν έχετε διαγνωστεί με κάποιο ψυχικό νόσημα, έχει διαγνωστεί πριν από το Πάρκινσον; <input type="checkbox"/> ναι <input type="checkbox"/> όχι	
<b>15</b>	Λοιπή φαρμακευτική αγωγή (εκτός Πάρκινσον)	Φάρμακα: Είναι σταθερή η αντικαταθλιπτική αγωγή τις τελευταίες 5 βδομάδες ή πρόκειται να αλλάξει σύντομα; <input type="checkbox"/> ναι <input type="checkbox"/> όχι	

<b>(Ε) ΟΙΚΟΓΕΝΕΙΑΚΟ ΙΑΤΡΙΚΟ ΙΣΤΟΡΙΚΟ</b>		
Γνωρίζετε αν κάποιος από την οικογένειά σας είχε κάποια πάθηση; Αν ναι, αναφέρατε πάθηση και βαθμό συγγένειας		
<b>01</b>	Καρδιολογική πάθηση	<input type="checkbox"/> όχι <input type="checkbox"/> ναι πάθηση: _____ συγγένεια: _____
<b>02</b>	Αναπνευστική πάθηση	<input type="checkbox"/> όχι <input type="checkbox"/> ναι πάθηση: _____ συγγένεια: _____
<b>03</b>	Νευρολογική πάθηση	<input type="checkbox"/> όχι <input type="checkbox"/> ναι πάθηση: _____ συγγένεια: _____
<b>04</b>	Μυοσκελετική πάθηση	<input type="checkbox"/> όχι <input type="checkbox"/> ναι πάθηση: _____ συγγένεια: _____
<b>05</b>	Άλλη πάθηση	<input type="checkbox"/> όχι <input type="checkbox"/> ναι πάθηση: _____ συγγένεια: _____

<b>(ΣΤ) ΕΓΚΡΙΣΗ / ΑΠΟΡΡΙΨΗ</b>	
<b>01</b>	<input type="checkbox"/> έγκριση ασθενή <input type="checkbox"/> απόρριψη ασθενή
<b>02</b>	Αν στην προηγούμενη ερώτηση επιλέξατε 'απόρριψη ασθενή', παρακαλώ αναφέρατε τον λόγο της απόρριψης:  <input type="checkbox"/> HADS-D < 8 <input type="checkbox"/> >3 H&Y στάδιο <input type="checkbox"/> 24< MMSE <input type="checkbox"/> πρόβλημα όρασης <input type="checkbox"/> πρόβλημα όρασης <input type="checkbox"/> δευτεροπαθές PD, παρκινσονισμός, εξωπυραμυδική συνδρομή <input type="checkbox"/> σωματική νόσος: <input type="checkbox"/> ψυχική νόσος: <input type="checkbox"/> εγχείρηση για Πάρκινσον

	<ul style="list-style-type: none"><li><input type="checkbox"/> άλλη εγχείρηση:</li><li><input type="checkbox"/> μη σταθερή φαρμακευτική αγωγή για Πάρκινσον</li><li><input type="checkbox"/> μη σταθερή φαρμακευτική αγωγή για κατάθλιψη</li><li><input type="checkbox"/> φάρμακα:</li><li><input type="checkbox"/> μη φαρμακολογική θεραπεία για Πάρκινσον:</li><li><input type="checkbox"/> αδυναμία παρακολούθησης προγράμματος</li><li><input type="checkbox"/> μη γνώση ελληνικών</li><li><input type="checkbox"/> άλλος λόγος:</li></ul>
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**Appendix 8.25. General Health Questionnaire (GHQ) (English version).**
**GENERAL HEALTH QUESTIONNAIRE (GHQ)**

<b>(A) BACKGROUND INFORMATION</b>					
<b>01</b>	Name				
<b>02</b>	Date		<b>03</b>	Patient's code	
<b>04</b>	Municipality		<b>05</b>	Telephone	
<b>06</b>	Occupation	<input type="checkbox"/> retired <input type="checkbox"/> household <input type="checkbox"/> unemployed <input type="checkbox"/> employee If 'employee', specify the occupation:			
<b>07</b>	Marital status	<input type="checkbox"/> married <input type="checkbox"/> separated <input type="checkbox"/> widower <input type="checkbox"/> single <input type="checkbox"/> divorced <input type="checkbox"/> in a relationship			
<b>08</b>	Language	<input type="checkbox"/> Greek <input type="checkbox"/> English <input type="checkbox"/> other: Do you know to read and write in Greek; <input type="checkbox"/> yes <input type="checkbox"/> no			
<b>09</b>	Will you be available for the entire period of study? (exercise programme and assessments) <input type="checkbox"/> yes <input type="checkbox"/> no				

<b>(B) ANTROPOMETRIC CHARACTERISTICS</b>					
<b>01</b>	Gender	<input type="checkbox"/> male <input type="checkbox"/> female			
<b>02</b>	Age (in years)		<b>03</b>	Height (in metres)	
<b>04</b>	Weight (in kilos)		<b>05</b>	BMI	
<b>06</b>	Nationality	<input type="checkbox"/> Greek <input type="checkbox"/> other:			

(C) MEDICAL HISTORY OF PD		
01	Disease	<input type="checkbox"/> PD <input type="checkbox"/> extrapyramidal syndrome <input type="checkbox"/> parkinsonian syndrome
02	Type of PD	<input type="checkbox"/> idiopathic (primary) <input type="checkbox"/> secondary
03	Medical diagnosis	<input type="checkbox"/> yes <input type="checkbox"/> no
04	How long have you been diagnosed with PD?	
05	H&Y stage	
06	PD pharmacological treatment	
07	Is your PD medication stable the last 4 weeks or is there any possibility to being changed shortly? <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> other:	
08	What hours of the day does your PD medication works best? / What hours of the day are you motor symptoms improved?	
09	Did you have any surgical operation (e.g.deep brain stimulation) due to PD? <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> in the future (when?: ..... )	
10	Do you receive any non-pharmacological treatment for PD? <input type="checkbox"/> yes <input type="checkbox"/> no If the answer is 'yes', specify: <input type="checkbox"/> physiotherapy/exercise <input type="checkbox"/> speech therapy <input type="checkbox"/> psychological intervention <input type="checkbox"/> diet <input type="checkbox"/> other : .....	

(D) HEALTH STATUS		
01	Smoking	<input type="checkbox"/> no <input type="checkbox"/> systematic smoker <input type="checkbox"/> social smoker <input type="checkbox"/> in the past
02	Walking	<input type="checkbox"/> independent <input type="checkbox"/> with an assistance device: Specify:
03	MMSE score	

<b>04</b>	Cardiovascular disease	<input type="checkbox"/> CHD <input type="checkbox"/> chest pain <input type="checkbox"/> myocardial infarction <input type="checkbox"/> hypertension <input type="checkbox"/> other. Specify:	
<b>05</b>	Respiratory disease	<input type="checkbox"/> COPD <input type="checkbox"/> asthma <input type="checkbox"/> other. Specify :	
<b>06</b>	Neurological disease	<input type="checkbox"/> stroke <input type="checkbox"/> other. Specify:	
<b>07</b>	Musculoskeletal disease	<input type="checkbox"/> cervical syndrome <input type="checkbox"/> low back pain <input type="checkbox"/> osteoarthritis <input type="checkbox"/> osteoporosis  <input type="checkbox"/> rheumatoid disease. Specify:  <input type="checkbox"/> injury. Specify:  <input type="checkbox"/> other. Specify:	
<b>08</b>	Other disease	<input type="checkbox"/> diabetes mellitus type I <input type="checkbox"/> dizziness <input type="checkbox"/> high cholesterol  <input type="checkbox"/> other. Specify:	
<b>09</b>	Surgical operation	<input type="checkbox"/> yes <input type="checkbox"/> no  If yes, what type of operation and when:	
<b>10</b>	Somatic pain	<input type="checkbox"/> yes <input type="checkbox"/> no  If yes, specify:	
<b>11</b>	Hearing /visual impairment	<input type="checkbox"/> yes <input type="checkbox"/> no  Specify:	
<b>12</b>	Falls during the last 2 months	<input type="checkbox"/> yes <input type="checkbox"/> no	
<b>13</b>	Do you follow any diet? <input type="checkbox"/> yes <input type="checkbox"/> no  If yes, state the reason:		
<b>14</b>	Mental disorders	<input type="checkbox"/> depression <input type="checkbox"/> anxiety  <input type="checkbox"/> Other. Specify: Have you been diagnosed with mental disorder before PD diagnosis? <input type="checkbox"/> yes <input type="checkbox"/> no	
<b>15</b>	Pharmacological treatment (apart from PD)	Medication:   Is your antidepressant medication stable the last 5 weeks or is there any possibility to being changed shortly? <input type="checkbox"/> yes <input type="checkbox"/> no	

(E) FAMILY'S MEDICAL HISTORY		
Do you know if a member of your family (relative) was/is suffering from a disease? If yes, specify the disease and the degree of relationship.		
<b>01</b>	Cardiovascular disease	<input type="checkbox"/> yes <input type="checkbox"/> no disease: degree of relationship:
<b>02</b>	Respiratory disease	<input type="checkbox"/> yes <input type="checkbox"/> no disease: degree of relationship:
<b>03</b>	Neurological disease	<input type="checkbox"/> yes <input type="checkbox"/> no disease: degree of relationship:
<b>04</b>	Musculoskeletal disease	<input type="checkbox"/> yes <input type="checkbox"/> no disease: degree of relationship:
<b>05</b>	Other disease	<input type="checkbox"/> yes <input type="checkbox"/> no disease: degree of relationship:

(G ) APPROVAL/REFUSAL	
<b>01</b>	<input type="checkbox"/> approval <input type="checkbox"/> refusal
<b>02</b>	Reason(s) of refusal: <input type="checkbox"/> HADS-D < 8 <input type="checkbox"/> >3 H&Y stage <input type="checkbox"/> 24< MMSE <input type="checkbox"/> visual impairment <input type="checkbox"/> hearing impairment <input type="checkbox"/> secondary PD, parkinsonian syndrome, extrapyramidal syndrome <input type="checkbox"/> somatic pain: <input type="checkbox"/> mental disorder: <input type="checkbox"/> surgical operation for PD: <input type="checkbox"/> other operation: <input type="checkbox"/> non stable PD medication <input type="checkbox"/> non stable antidepressant medication



	<input type="checkbox"/> pharmacological treatment: <input type="checkbox"/> non pharmacological treatment for PD: <input type="checkbox"/> inability to participate <input type="checkbox"/> inability to write or read in Greek <input type="checkbox"/> other reason:
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**Appendix 8.26.** Descriptions of clinical examinations and calculations for the record of somatometric characteristics.

*Clinical examination for height*

The height was measured without shoes, with the feet together, standing as tall as possible and looking straight ahead, with the back placed firmly against a wall, using a metre (García-Río et al., 2013; Kleisouras, 1997). In the case of chest deformities, the span was measured (crossed arms from middle finger to middle finger), estimating the height from the following ratio:  $\text{height} = \text{span} / 1.06$  (Parker et al., 1996).

*Clinical examination for weight*

The weight was measured with a digital bathroom scale (Tanita HD-380). The individual stood with minimal movement with hands by their side. Shoes and excess clothing were removed (Kleisouras, 1997).

*Calculation of the BMI*

The equation  $\text{weight (in kilos)} / \text{height}^2 \text{ (in metres)}$  calculated the BMI of each participant (Kleisouras, 1997).

\* The above tests and calculations were performed by the chief investigator

**Appendix 8.27.** Description of the Snijders and Bloem FOG Test.

The instructions for the Snijders and Bloem FOG Test were given by the chief investigator. The patients were asked to perform repeated 360° narrow turns, in both directions, at high speed (Snijders et al., 2012). The examination included turning in both directions, because FOG often shows a directional sensitivity, and it is sometimes present just in a rightward or leftward direction (Snijders et al., 2008). Eight alternate full turns (four into each direction) were performed for the classification of freezers and non-freezers. If this did not provoke freezing, dual tasks were added to the test while performing four alternate full turns into each direction. Participants were asked to count while turning (Snijders et al., 2012). The researcher demonstrated first the test to the participants. The only given instructions during the test were: 'turn right' and 'turn left'. If FOG was observed, the individual was recorded as freezer.

Special emphasis was given to differentiate FOG from festination. In FOG, there is a complete stop and the patient experiences the feeling of 'being glued to the floor'. During festination, there is a progressive decrease in step length and increase in cadence, whereas the characteristic 'magnetic feeling' under the feet is not present (Snijders et al., 2008).

No instructions were given during the test performance, except the initial order 'go'. On a data sheet the time to complete the test was recorded, and qualitative aspects of walking (such as freezing, no arms swinging) were ticked.

## Appendix 8.28. 'Snijders and Bloem FOG Test' form (Greek version)

**ΤΕΣΤ ΠΑΓΩΜΑΤΟΣ 'SNIJDERS AND BLOEM'**

Όνομα: .....

Ημερομηνία: .....

**Μεμονωμένη δραστηριότητα**

Αν ισχύει κάτι από τα παρακάτω, σημειώσατε με (X).

1. 'Στρίψε αριστερά' : ☐ πάγωμα
2. 'Στρίψε δεξιά': ☐ πάγωμα
3. 'Στρίψε αριστερά' : ☐ πάγωμα
4. 'Στρίψε δεξιά': ☐ πάγωμα
5. 'Στρίψε αριστερά' : ☐ πάγωμα
6. 'Στρίψε δεξιά': ☐ πάγωμα
7. 'Στρίψε αριστερά' : ☐ πάγωμα
8. 'Στρίψε δεξιά': ☐ πάγωμα

**Διπλή δραστηριότητα**

Αν ισχύει κάτι από τα παρακάτω, σημειώσατε με (X).

1. 'Στρίψε αριστερά' : ☐ πάγωμα
2. 'Στρίψε δεξιά': ☐ πάγωμα
3. 'Στρίψε αριστερά' : ☐ πάγωμα
4. 'Στρίψε δεξιά': ☐ πάγωμα
5. 'Στρίψε αριστερά' : ☐ πάγωμα
6. 'Στρίψε δεξιά': ☐ πάγωμα
7. 'Στρίψε αριστερά' : ☐ πάγωμα
8. 'Στρίψε δεξιά': ☐ πάγωμα

Ο ασθενής εμφανίζει πάγωμα: ☐ Ναι☐ Όχι

**Appendix 8.29. 'Snijders and Bloem FOG Test' form (English version)****SNIJDERS AND BLOEM FOG test****Name:** .....**Date:** .....**Single task**

If any of the following is true, please tick (X):

1. 'Turn left' :     ☐ FOG
2. 'Turn right':    ☐ FOG
3. 'Turn left' :     ☐ FOG
4. 'Turn right':    ☐ FOG
5. 'Turn left' :     ☐ FOG
6. 'Turn right':    ☐ FOG
7. 'Turn left' :     ☐ FOG
8. 'Turn right':    ☐ FOG

**Dual task**

If any of the following is true, please tick (X):

1. 'Turn left' :     ☐ FOG
2. 'Turn right':    ☐ FOG
3. 'Turn left' :     ☐ FOG
4. 'Turn right':    ☐ FOG
5. 'Turn left' :     ☐ FOG
6. 'Turn right':    ☐ FOG
7. 'Turn left' :     ☐ FOG
8. 'Turn right':    ☐ FOG

**The patient is:** ☐ freezer     ☐ non-freezer

**Appendix 8.30.** Description of the Parkinson's Disease Questionnaire 39 (PDQ-39).

The PDQ-39 is a 39-item self-report questionnaire, which assesses the QoL of PD patients over the last month. The questions, which are clustered in eight subscales (table A.1), have five ordinal response options, rating from zero (never) to four (always) (Sampaio et al., 2012).

**Table A.1.** The eight subscales of the PDQ-39 and the number of included items.

Subscales	Number of items
Mobility	10 (items: 1-10)
ADLs	6 (items: 11-16)
Emotional well-being	6 (items: 17-22)
Stigma	4 (items: 23-26)
Social support	3 (items: 27-29)
Cognition	4 (items: 30-33)
Communication	3 (items: 34-36)
Bodily discomfort	3 (items: 37-39)

*Abbreviations. ADLs: activities of daily living.*

Scores can be calculated for each dimension (subscale) (dimension score), and for the whole test (PDQ-39 Summary Index- PDQ-39 SI) to assess the overall health-related QoL. Each dimension score ranges from zero (never have difficulty) to 100 (always have difficulty), with lower scores reflecting better QoL. The dimension score is the sum of scores of all the items in the dimension, divided by the maximum possible score of all the items in the dimension, multiplied by 100. The PDQ-39 SI is the sum of dimensions total scores divided by eight (Jenkinson et al., 1997; Sampaio et al., 2012).

## Appendix 8.31. Parkinson's Disease Questionnaire 39 (PDQ-39) (Greek version)

**ΕΡΩΤΗΜΑΤΟΛΟΓΙΟ ΠΟΙΟΤΗΤΑΣ ΖΩΗΣ ΣΤΟ ΠΑΡΚΙΝΣΟΝ (PDQ-39)**

Όνομα:.....

Ημερομηνία: .....

Παρακαλώ συμπληρώστε το παρακάτω ερωτηματολόγιο. Σημειώστε με Χ μία απάντηση σε κάθε ερώτηση.

Εξαιτίας του Πάρκινσον πόσο συχνά τον τελευταίο μήνα.....		Ποτέ	Περιστασιακά	Μερικές φορές	Συχνά	Πάντα ή δεν μπορώ καθόλου
01	Είχατε δυσκολία να κάνετε τις δραστηριότητες αναψυχής που θα θέλατε;					
02	Είχατε δυσκολία να φροντίσετε το σπίτι σας (π.χ. δουλειές του σπιτιού, μαγείρεμα);					
03	Είχατε δυσκολία να μεταφέρετε τσάντες με ψώνια;					
04	Είχατε δυσκολία να περπατήσετε μισό χιλιόμετρο;					
05	Είχατε δυσκολία να περπατήσετε 100 μέτρα;					
06	Είχατε δυσκολία να περπατήσετε μέσα στο σπίτι σας όσο εύκολα θα θέλατε;					
07	Είχατε δυσκολία να περπατήσετε σε δημόσιο χώρο;					
08	Χρειάζοσασταν κάποιον να σας συνοδεύσει όταν πηγαίνατε έξω;					
09	Είχατε φόβο η ανησυχία μήπως πέσετε σε δημόσιο χώρο;					
10	Είχατε περιοριστεί εντός σπιτιού περισσότερο απ' όσο θα θέλατε;					

Εξαιτίας του Πάρκινσον πόσο συχνά τον τελευταίο μήνα.....		Ποτέ	Περιστασιακά	Μερικές φορές	Συχνά	Πάντα ή δεν μπορώ καθόλου
11	Είχατε δυσκολία να πλυθείτε μόνος σας;					
12	Είχατε δυσκολία να ντυθείτε μόνος σας;					
13	Είχατε δυσκολία να δέσετε τα κορδόνια των παπουτσιών σας;					
14	Είχατε πρόβλημα να γράψετε καθαρά;					
15	Είχατε δυσκολία να κόψετε το φαγητό σας;					
16	Είχατε δυσκολία να κρατήσετε ένα ποτήρι με νερό χωρίς να το χύσετε;					
17	Νιώσατε θλιμμένος;					
18	Αισθανθήκατε απομονωμένος και μόνος;					
19	Δακρύσατε ή κλάψατε;					
20	Νιώσατε θυμωμένος ή πικραμένος;					
21	Νιώσατε αγχωμένος;					
22	Είχατε ανησυχία για το μέλλον σας;					
23	Αισθανθήκατε ότι έπρεπε να κρύψετε την ασθένειά σας από άλλους ανθρώπους;					
24	Αποφύγατε καταστάσεις που περιλαμβάνουν φαγητό ή ποτό σε δημόσιο χώρο;					
25	Νοιώσατε άσχημα σε δημόσιο χώρο λόγω της ασθένειάς σας;					
26	Είχατε ανησυχία εξαιτίας της αντίδρασης των άλλων ανθρώπων σε εσάς;					
27	Είχατε πρόβλημα με τις στενές προσωπικές σας σχέσεις;					
28	Δεν είχατε υποστήριξη όπως θα θέλατε από τον σύζυγό σας ή τον σύντροφό σας; Αν δεν έχετε σύντροφο ή σχέση σημειώσατε με Χ εδώ.					
29	Δεν είχατε υποστήριξη όπως θα θέλατε από την οικογένειά σας ή στενούς φίλους;					
30	Αποκοιμηθήκατε απροσδόκητα κατά την διάρκεια της ημέρας;					
31	Είχατε προβλήματα με την συγκέντρωσή σας (π.χ. όταν διαβάζατε ή όταν βλέπατε τηλεόραση);					



Εξαιτίας του Πάρκινσον πόσο συχνά τον τελευταίο μήνα.....		Ποτέ	Περιστασιακά	Μερικές φορές	Συχνά	Πάντα ή δεν μπορώ καθόλου
32	Αισθανθήκατε ότι η μνήμη σας ήταν κακή;					
33	Είχατε εφιάλτες ή παραισθήσεις;					
34	Είχατε δυσκολία με την ομιλία σας;					
35	Αισθανθήκατε ανίκανος να επικοινωνήσετε με τους άλλους ανθρώπους καθαρά;					
36	Αισθανθήκατε ότι οι άλλοι άνθρωποι σας αγνοούν;					
37	Είχατε επώδυνες μυϊκές κράμπες ή σπασμούς;					
38	Είχατε πόνο στις αρθρώσεις ή στο σώμα σας;					
39	Νιώσατε αφόρητη ζέστη ή κρύο;					

**Ελέγξτε ότι έχετε απαντήσει όλες τις ερωτήσεις. Σας ευχαριστούμε για την συμμετοχή σας.**

**Appendix 8.32. Parkinson's Disease Questionnaire 39 (PDQ-39) (English version)****PDQ-39 QUESTIONNAIRE****Name:**.....**Date:** .....**Please complete the following questionnaire. Tick one box for each question.**

Due to having Parkinson's disease, how often during the last month have you....		Never	Occasionally	Sometimes	Often	Always or cannot at all
<b>01</b>	Had difficulty doing the leisure activities which you would like to do?					
<b>02</b>	Had difficulty looking after your home, e.g. DIY, housework, cooking?					
<b>03</b>	Had difficulty carrying bags of shopping?					
<b>04</b>	Had problems walking half a mile?					
<b>05</b>	Had problems walking 100 yards?					
<b>06</b>	Had problems getting around the house as easily as you would like?					
<b>07</b>	Had difficulty getting around in public?					
<b>08</b>	Needed someone else to accompany you when you went out?					
<b>09</b>	Felt frightened or worried about falling over in public?					
<b>10</b>	Been confined to the house more than you would like?					
<b>11</b>	Had difficulty washing yourself?					
<b>12</b>	Had difficulty dressing yourself?					

Due to having Parkinson's disease, how often during the last month have you....		Never	Occasionally	Sometimes	Often	Always or cannot at all
13	Had problems doing up your shoe laces?					
14	Had problems writing clearly?					
15	Had difficulty cutting up your food?					
16	Had difficulty holding a drink without spilling it?					
17	Felt depressed?					
18	Felt isolated and lonely?					
19	Felt weepy or tearful?					
20	Felt angry or bitter?					
21	Felt anxious?					
22	Felt worried about your future?					
23	Felt you had to conceal your Parkinson's from people?					
24	Avoided situations which involve eating or drinking in public?					
25	Felt embarrassed in public due to having Parkinson's disease?					
26	Felt worried by other people's reaction to you?					
27	Had problems with your close personal relationships?					
28	Lacked support in the ways you need from your spouse or partner?					
	If you do not have a spouse or partner tick here					
29	Lacked support in the ways you need from your family or close friends?					
30	Unexpectedly fallen asleep during the day?					
31	Had problems with your concentration, e.g. when reading or watching TV?					
32	Felt your memory was bad?					
33	Had distressing dreams or hallucinations?					
34	Had difficulty with your speech?					

Due to having Parkinson's disease, how often during the last month have you....		Never	Occasionally	Sometimes	Often	Always or cannot at all
<b>35</b>	Felt unable to communicate with people properly?					
<b>36</b>	Felt ignored by people?					
<b>37</b>	Had painful muscle cramps or spasms?					
<b>38</b>	Had aches and pains in your joints or body?					
<b>39</b>	Felt unpleasantly hot or cold?					

**Thank you for completing the PDQ 39 questionnaire!**

**Appendix 8.33.** Description of the Berg Balance Scale (BBS).

The BBS is a clinical test, which was originally designed for use in the elderly population. It is a 14-item scale evaluating the ability to maintain balance in different positions, postural changes and movements. Each item is scored on a five-point ordinal scale ranging from zero to four, including a variety of tasks. Zero indicates the lowest level of function (unable to perform) and four the highest level (normal performance). The possible highest total score of the scale is 56, indicating excellent balance (Berg, 1989).

In the current study, single trials of BBS were performed, without the use of walking aid, similarly to the study by Dibble et al. (2008). Basic equipment was used for the test: a chair without armrests (chair height: 45- 47.5 cm), a chair with armrests (chair height: 45.5-47 cm; arm height: 65-67.5 cm), a stopwatch, a ruler, an item on the floor (pencil), and a step stool (step stool height: 22 cm). All tasks were demonstrated before by the researcher, to ensure that participants had understood how to perform the activity. Then, he gave instructions to participants to perform the tasks. The tasks were performed closed to the wall or stable furniture for safety reasons: to avoid falls and fall-related injuries. The participants were allowed to rest for a while between the tasks, if needed (Steffen and Seney, 2008).

Special attention was given to items eight (reaching forward with outstretched arm while standing); and 14 (standing on one leg) of the scale. Item eight was performed closed on the wall. The participant was instructed not to touch the wall. A stripe was placed on the wall for the guidance of participant's hand during the task. Before the start of the task, the tip of his third finger were placed on the edge of the stripe. Regarding item 14, the participants was allowed for a few moment to determine which leg would use for the test.

## Appendix 8.34. Berg Balance Scale (BBS) (Greek version)

ΚΛΙΜΑΚΑ  
ΙΣΟΡΡΟΠΙΑΣ  
BERG

Όνομα: \_\_\_\_\_

Ημερομηνία: \_\_\_\_\_

Δοκιμασίες ισορροπίαςScore (0-4)

- |  |       |
|--|-------|
| 1. Από καθιστή σε όρθια θέση   | _____ |
| 2. Όρθια θέση χωρίς υποστήριξη   | _____ |
| 3. Κάθισμα χωρίς υποστήριξη  | _____ |
| 4. Από όρθια σε καθιστή θέση   | _____ |
| 5. Μεταφορές   | _____ |
| 6. Όρθιος χωρίς υποστήριξη με τα μάτια κλειστά                               | _____ |
| 7. Όρθιος χωρίς υποστήριξη με τα πόδια ενωμένα                               | _____ |
| 8. Σκύψιμο προς τα εμπρός με τεντωμένο το χέρι από<br>όρθια θέση             | _____ |
| 9. Άρση αντικειμένου από το πάτωμα από όρθια θέση                            | _____ |
| 10. Στροφή κεφαλής και κορμού προς τα πίσω από<br>όρθια θέση                 | _____ |
| 11. Στροφή 360 μοιρών από όρθια θέση   | _____ |
| 12. Τοποθέτηση των ποδιών εναλλάξ σε σκαλοπάτι ή<br>σε σκαμνί από όρθια θέση | _____ |
| 13. Όρθια θέση χωρίς υποστήριξη με το ένα πόδι<br>εμπρός                     | _____ |
| 14. Μονοποδική στήριξη σε όρθια θέση   | _____ |

ΣΥΝΟΛΟ (0-56): \_\_\_\_\_

Ερμηνεία

- |       |                         |
|-------|-------------------------|
| 0-20  | Υψηλός κίνδυνος πτώσης  |
| 21-40 | μέτριος κίνδυνος πτώσης |
| 41-56 | χαμηλός κίνδυνος πτώσης |

## ΔΟΚΙΜΑΣΙΕΣ ΚΛΙΜΑΚΑΣ ΙΣΣΟΡΟΠΙΑΣ BERG

01	<p><b>ΑΠΟ ΚΑΘΙΣΤΗ ΣΕ ΟΡΘΙΑ ΘΕΣΗ</b>  <b>Οδηγίες:</b> Σηκωθείτε και προσπαθήστε να μην χρησιμοποιήσετε τα χέρια σας για υποστήριξη.</p> <p>( ) 4 Μπορεί να σταθεί χωρίς να χρησιμοποιήσει τα χέρια και να σταθεί ανεξάρτητα.  ( ) 3 Είναι σε θέση να σταθεί ανεξάρτητα με τα χέρια.  ( ) 2 Είναι σε θέση να σταθεί χρησιμοποιώντας τα χέρια μετά από αρκετές δοκιμές.  ( ) 1 Χρειάζεται ελάχιστη βοήθεια για να σταθεί ή να σταθεροποιηθεί.  ( ) 0 Χρειάζεται μέτρια ή μέγιστη βοήθεια για να σηκωθεί.</p>
02	<p><b>ΟΡΘΙΑ ΘΕΣΗ ΧΩΡΙΣ ΥΠΟΣΤΗΡΙΞΗ</b>  <b>Οδηγίες:</b> Προσπαθήστε να σταθείτε 2 λεπτά χωρίς να κρατηθείτε.</p> <p>( ) 4 Είναι σε θέση να σταθεί με ασφάλεια για 2 λεπτά.  ( ) 3 Είναι σε θέση να σταθεί για 2 λεπτά με επίβλεψη.  ( ) 2 Είναι σε θέση να σταθεί για 30 δευτερόλεπτα χωρίς υποστήριξη.  ( ) 1 Χρειάζεται αρκετές προσπάθειες για να σταθεί 30 δευτερόλεπτα χωρίς βοήθεια.  ( ) 0 Αδυνατεί να σταθεί για 30 δευτερόλεπτα χωρίς βοήθεια.</p> <p><b>Αν είναι σε θέση να σταθεί με ασφάλεια για 2 λεπτά προχωρήστε στο βήμα 4.</b></p>
03	<p><b>ΚΑΘΙΣΜΑ ΜΕ ΤΗΝ ΠΛΑΤΗ ΝΑ ΜΗΝ ΑΚΟΥΜΠΑΕΙ ΚΑΠΟΥ ΚΑΙ ΜΕ ΤΑ ΠΟΔΙΑ ΝΑ ΣΤΗΡΙΖΟΝΤΑΙ ΣΤΟ ΔΑΠΕΔΟ Ή ΣΕ ΣΚΑΜΠΟ</b>  <b>Οδηγίες:</b> Να καθίσετε με σταυρωμένα τα χέρια για 2 λεπτά.</p> <p>( ) 4 Είναι σε θέση να καθίσει με ασφάλεια και σιγουριά για 2 λεπτά.  ( ) 3 Είναι σε θέση να καθίσει για 2 λεπτά με επίβλεψη.  ( ) 2 Είναι σε θέση να καθίσει για 30 δευτερόλεπτα.  ( ) 1 Είναι σε θέση να καθίσει για 10 δευτερόλεπτα.  ( ) 0 Δεν είναι σε θέση να καθίσει για 10 δευτερόλεπτα χωρίς υποστήριξη.</p>
04	<p><b>ΑΠΟ ΟΡΘΙΑ ΣΕ ΚΑΘΙΣΤΗ ΘΕΣΗ</b>  <b>Οδηγίες:</b> Παρακαλώ να καθίσετε.</p> <p>( ) 4 Κάθεται με ασφάλεια με ελάχιστη χρήση των χεριών.  ( ) 3 Ελέγχει τον τρόπο που κάθεται χρησιμοποιώντας τα χέρια.  ( ) 2 Χρησιμοποιεί το πίσω μέρος των ποδιών για ελέγξει το κάθισμα.  ( ) 1 Κάθεται ανεξάρτητα, αλλά ανεξέλεγκτα.  ( ) 0 Χρειάζεται βοήθεια για να καθίσει.</p>
05	<p><b>ΜΕΤΑΦΟΡΕΣ</b>  <b>Οδηγίες:</b> Δυο καρέκλες, μία με μπράτσα και η άλλη χωρίς μπράτσα, σε γωνία 90 μοιρών μεταξύ τους. Ζητήστε από τον εξεταζόμενο να μεταφερθεί από τη μια καρέκλα στην άλλη, με όσον το δυνατό λιγότερη στήριξη. Έπειτα πρέπει να μεταφερθεί στην αρχική του θέση, δηλαδή προς την αντίθετη κατεύθυνση.</p> <p>( ) 4 Μπορεί να μεταφερθεί με ασφάλεια με μικρή χρήση των χεριών.  ( ) 3 Μπορεί να μεταφέρει με ασφάλεια με σαφή χρήση των χεριών.  ( ) 2 Μπορεί να μεταφέρει με καθοδήγηση ή εποπτεία.  ( ) 1 Χρειάζεται βοήθεια από ένα άτομο.  ( ) 0 Χρειάζεται βοήθεια από δύο άτομα ή εποπτεία για να είναι ασφαλής.</p>

06	<p><b>ΟΡΘΙΟΣ ΧΩΡΙΣ ΥΠΟΣΤΗΡΙΞΗ ΜΕ ΤΑ ΜΑΤΙΑ ΚΛΕΙΣΤΑ</b>  <b>Οδηγίες:</b> Κλείστε τα μάτια σας και μείνετε ακίνητος για 10 δευτερόλεπτα.  <input type="checkbox"/> 4 Είναι σε θέση να σταθεί με ασφάλεια για 10 δευτερόλεπτα.  <input type="checkbox"/> 3 Είναι σε θέση να σταθεί για 10 δευτερόλεπτα με εποπτεία.  <input type="checkbox"/> 2 Είναι σε θέση να σταθεί για 3 δευτερόλεπτα.  <input type="checkbox"/> 1 Δεν είναι σε θέση να κλείσει τα μάτια για 3 δευτερόλεπτα αλλά παραμένει σταθερός.  <input type="checkbox"/> 0 Χρειάζεται βοήθεια για να μην πέσει.</p>
07	<p><b>ΟΡΘΙΟΣ ΧΩΡΙΣ ΥΠΟΣΤΗΡΙΞΗ ΜΕ ΤΑ ΠΟΔΙΑ ΕΝΩΜΕΝΑ</b>  <b>Οδηγίες:</b> Τοποθετήστε τα πόδια σας μαζί, το ένα δίπλα στο άλλο, και σταθείτε χωρίς βοήθεια.  <input type="checkbox"/> 4 Είναι σε θέση να τοποθετήσει τα πόδια του ενωμένα ανεξάρτητα και να σταθεί για 1 λεπτό με ασφάλεια.  <input type="checkbox"/> 3 Είναι σε θέση να τοποθετήσει τα πόδια του ενωμένα ανεξάρτητα και να σταθεί για 1 λεπτό με επίβλεψη.  <input type="checkbox"/> 2 Είναι σε θέση να τοποθετήσει τα πόδια του ενωμένα ανεξάρτητα αλλά δεν μπορεί να σταθεί για 30 δευτερόλεπτα.  <input type="checkbox"/> 1 Χρειάζεται βοήθεια για να πετύχει τη σωστή θέση αλλά μπορεί να σταθεί για 15 δευτερόλεπτα.  <input type="checkbox"/> 0 Χρειάζεται βοήθεια για να πετύχει τη σωστή θέση και δεν μπορεί να σταθεί για 15 δευτερόλεπτα</p>
08	<p><b>ΣΚΥΨΙΜΟ ΠΡΟΣ ΤΑ ΕΜΠΡΟΣ ΜΕ ΤΕΝΤΩΜΕΝΟ ΤΟ ΧΕΡΙ ΑΠΟ ΟΡΘΙΑ ΘΕΣΗ</b>  <b>Οδηγίες:</b> Σηκώστε το χέρι σε 90 μοίρες. Τεντώστε τα δάχτυλα σας και φτάστε όσο πιο μακριά μπορείτε. (Ο εξεταστής τοποθετεί ένα χάρακα στο τέλος των δάχτυλων όταν το χέρι είναι σε 90 μοίρες. Τα δάχτυλα δεν πρέπει να αγγίζουν το χάρακα ενώ φτάνει προς τα εμπρός. Η καταγραφή της μέτρησης είναι η απόσταση από όπου φτάνουν τα δάχτυλα έως το σημείο που είναι τοποθετημένο σε μια κοντινή απόσταση. Όταν είναι δυνατό, μπορεί να ζητηθεί η χρήση και των 2 χεριών ώστε να αποφευχθεί η περιστροφή του κορμού.)  <input type="checkbox"/> 4 Μπορεί να φτάσει με ασφάλεια προς τα εμπρός &gt; 25 cm ( 10 ίντσες).  <input type="checkbox"/> 3 Μπορεί να φτάσει με ασφάλεια προς τα εμπρός &gt; 12 cm ( 5 ίντσες).  <input type="checkbox"/> 2 Μπορεί να φτάσει με ασφάλεια προς τα εμπρός &gt; 5 cm ( 2 ίντσες).  <input type="checkbox"/> 1 Μπορεί να φτάσει προς τα εμπρός αλλά χρειάζεται εποπτεία.  <input type="checkbox"/> 0 Χάνει την ισορροπία ενώ προσπαθεί / χρειάζεται εξωτερική υποστήριξη.</p>
09	<p><b>ΑΡΣΗ ΑΝΤΙΚΕΙΜΕΝΟΥ ΑΠΟ ΤΟ ΠΑΤΩΜΑ ΑΠΟ ΟΡΘΙΑ ΘΕΣΗ</b>  <b>Οδηγίες:</b> Σηκώστε το αντικείμενο που βρίσκεται μπροστά από τα πόδια σας  <input type="checkbox"/> 4 Είναι σε θέση να το σηκώσει με ασφάλεια και ευκολία.  <input type="checkbox"/> 3 Είναι σε θέση να το σηκώσει με ασφάλεια αλλά χρειάζεται εποπτεία.  <input type="checkbox"/> 2 Αδυνατεί να το σηκώσει αλλά φτάνει στα 2-5 εκατοστά από το αντικείμενο και κρατά την ισορροπία ανεξάρτητα.  <input type="checkbox"/> 1 Δεν είναι σε θέση να το σηκώσει και χρειάζεται επίβλεψη ενώ προσπαθεί.  <input type="checkbox"/> 0 Αδυνατεί να δοκιμάσει για να μη χάσει την ισορροπία ή πέσει.</p>



10	<p><b>ΣΤΡΟΦΗ ΚΕΦΑΛΗΣ ΚΑΙ ΚΟΡΜΟΥ ΠΡΟΣ ΤΑ ΠΙΣΩ ΑΠΟ ΟΡΘΙΑ ΘΕΣΗ</b></p> <p><b>Οδηγίες:</b> Στρίψτε (κεφάλι και κορμό) όσο περισσότερο μπορείτε αριστερά και προσπαθήστε να κοιτάξετε πίσω σας. Επαναλάβετε το ίδιο από τα δεξιά. (Ο εξεταστής τοποθετώντας ένα αντικείμενο πίσω από τον εξεταζόμενο, τον ενθαρρύνει να κάνει καλύτερη στροφή.)</p> <p>( ) 4 Κοιτάζει πίσω από τις δύο πλευρές και το βάρος μετατοπίζεται καλά.</p> <p>( ) 3 Κοιτάζει πίσω από τη μια πλευρά μόνο και η άλλη πλευρά δείχνει μικρότερη μετατόπιση βάρους.</p> <p>( ) 2 Γυρνάει μόνο προς τα πλάγια, αλλά διατηρεί την ισορροπία.</p> <p>( ) 1 Χρειάζεται επίβλεψη κατά την περιστροφή.</p> <p>( ) 0 Χρειάζεται βοήθεια για να μη χάσει την ισορροπία ή για να μη πέσει.</p>
11	<p><b>ΣΤΡΟΦΗ 360 ΜΟΙΡΩΝ ΑΠΟ ΟΡΘΙΑ ΘΕΣΗ</b></p> <p><b>Οδηγίες:</b> Κάνετε μια ολοκληρωμένη στροφή γύρω από τον εαυτό σας. Παύση. Έπειτα κάνετε μια ολοκληρωμένη στροφή προς την αντίθετη κατεύθυνση.</p> <p>( ) 4 Είναι σε θέση να γυρίσει 360 μοίρες με ασφάλεια σε 4 δευτερόλεπτα ή και λιγότερο.</p> <p>( ) 3 Είναι σε θέση να γυρίσει 360 μοίρες με ασφάλεια σε μια πλευρά μόνο σε 4 δευτερόλεπτα ή και λιγότερο.</p> <p>( ) 2 Είναι σε θέση να γυρίσει 360 μοίρες με ασφάλεια, αλλά σιγά σιγά.</p> <p>( ) 1 Χρειάζεται στενή επίβλεψη ή καθοδήγηση.</p> <p>( ) 0 Χρειάζεται βοήθεια ενώ γυρνάει.</p>
12	<p><b>ΤΟΠΟΘΕΤΗΣΗ ΤΩΝ ΠΟΔΙΩΝ ΕΝΑΛΛΑΞ ΣΕ ΣΚΑΛΟΠΑΤΙΉ ΣΕ ΣΚΑΜΝΙ ΑΠΟ ΟΡΘΙΑ ΘΕΣΗ ΧΩΡΙΣ ΣΤΗΡΙΓΜΑ</b></p> <p><b>Οδηγίες:</b> Τοποθετήστε το κάθε πόδι εναλλάξ σε ένα σκαλοπάτι/ σκαμνί, ενώ είστε σε όρθια θέση χωρίς στήριγμα Συνεχίστε μέχρι το κάθε πόδι να ακουμπήσει το σκαλοπάτι/ σκαμνί για 4 φορές.</p> <p>( ) 4 Είναι σε θέση να σταθεί ανεξάρτητα και με ασφάλεια και να ολοκληρώσει 8 βήματα σε 20 δευτερόλεπτα.</p> <p>( ) 3 Είναι σε θέση να σταθεί ανεξάρτητος και να ολοκληρώσει 8 βήματα σε περισσότερο από 20 δευτερόλεπτα.</p> <p>( ) 2 Είναι σε θέση να ολοκληρώσει 4 βήματα, χωρίς βοήθεια, με εποπτεία.</p> <p>( ) 1 Είναι σε θέση να ολοκληρώσει πάνω από 2 βήματα με ελάχιστη βοήθεια.</p> <p>( ) 0 Δεν είναι σε θέση να δοκιμάσει / χρειάζεται βοήθεια για να μην πέσει.</p>
13	<p><b>ΟΡΘΙΑ ΘΕΣΗ ΧΩΡΙΣ ΥΠΟΣΤΗΡΙΞΗ ΜΕ ΤΟ ΕΝΑ ΠΟΔΙ ΕΜΠΡΟΣ</b></p> <p><b>Οδηγίες:</b> (Υπόδειξη στον εξεταζόμενο). Τοποθετήστε το ένα πόδι στην ευθεία μπροστά από το άλλο. Αν αισθάνεστε ότι δεν μπορείτε, προσπαθήστε να κάνετε ένα βήμα αρκετά μακριά στην ευθεία έτσι ώστε η φτέρνα από το μπροστινό πόδι να είναι στην ευθεία από τα δάχτυλα του άλλου ποδιού. (Για 3 βαθμούς το μήκος του βήματος θα πρέπει να υπερβαίνει το μήκος άλλου ποδιού)</p> <p>( ) 4 Είναι ικανός να κρατήσει τα πόδια του παράλληλα και ανεξάρτητα και να κρατηθεί για 30 δευτερόλεπτα.</p> <p>( ) 3 Είναι σε θέση να τοποθετήσει το ένα πόδι μπροστά από το άλλο ανεξάρτητα και να κρατηθεί για 30 δευτερόλεπτα.</p> <p>( ) 2 Είναι σε θέση να κάνει μικρό βήμα ανεξάρτητα και να κρατηθεί για 30 δευτερόλεπτα.</p> <p>( ) 1 Χρειάζεται βοήθεια για να κάνει βήμα αλλά μπορεί να κρατηθεί για 15 δευτερόλεπτα.</p> <p>( ) 0 Χάνει την ισορροπία του ενώ στέκεται ή περπατάει</p>

14	<p><b>ΜΟΝΟΠΟΔΙΚΗ ΣΤΗΡΙΞΗ ΣΕ ΟΡΘΙΑ ΘΕΣΗ</b></p> <p><b>Οδηγίες: Σταθείτε στο ένα πόδι όσο μπορείτε χωρίς βοήθεια.</b></p> <p>( ) 4 Είναι σε θέση να σηκώσει το πόδι ανεξάρτητα και να σταθεί για περισσότερο από 10 δευτερόλεπτα.</p> <p>( ) 3 Είναι σε θέση να σηκώσει το πόδι ανεξάρτητα και να σταθεί για 5-10 δευτερόλεπτα.</p> <p>( ) 2 Είναι σε θέση να σηκώσει το πόδι ανεξάρτητα και να σταθεί για περισσότερο από 3 δευτερόλεπτα.</p> <p>( ) 1 Προσπαθεί να σηκώσει το πόδι αλλά δεν είναι σε θέση να το κρατήσει πάνω από 3 δευτερόλεπτα, αλλά εξακολουθεί να στέκεται ανεξάρτητα.</p> <p>( ) 0 Αδυνατεί να δοκιμάσει ή χρειάζεται βοήθεια για την πρόληψη των πτώσεων.</p>
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**Appendix 8.35. Berg Balance Scale (BBS) (English version)**

**BERG  
BALANCE  
SCALE**

**Name:** \_\_\_\_\_

**Date:** \_\_\_\_\_

<b>Item description</b>	<b>Score (0-4)</b>
-------------------------	--------------------

- |   |       |
|---|-------|
| 1. Sitting to standing                    | _____ |
| 2. Standing unsupported                   | _____ |
| 3. Sitting unsupported                    | _____ |
| 4. Standing to sitting                    | _____ |
| 5. Transfers                              | _____ |
| 6. Standing with eyes closed              | _____ |
| 7. Standing with feet together            | _____ |
| 8. Reaching forward with outstretched arm | _____ |
| 9. Retrieving object from floor           | _____ |
| 10. Turning to look behind                | _____ |
| 11. Turning 360 degrees                   | _____ |
| 12. Placing alternate foot on stool       | _____ |
| 13. Standing with one foot in front       | _____ |
| 14. Standing on one foot                  | _____ |

**TOTAL (0-56):** \_\_\_\_\_

**Interpretation**

- 41-56 = low fall risk
- 21-40 = medium fall risk
- 0-20 = high fall risk

**BERG BALANCE SCALE TASKS**

<b>01</b>	<b>SITTING TO STANDING</b> <b>INSTRUCTIONS: Please stand up. Try not to use your hand for support.</b>  ( ) 4 able to stand without using hands and stabilize independently ( ) 3 able to stand independently using hands ( ) 2 able to stand using hands after several tries ( ) 1 needs minimal aid to stand or stabilize ( ) 0 needs moderate or maximal assist to stand
<b>02</b>	<b>STANDING UNSUPPORTED</b> <b>INSTRUCTIONS: Please stand for two minutes without holding on.</b>  ( ) 4 able to stand safely for 2 minutes ( ) 3 able to stand 2 minutes with supervision ( ) 2 able to stand 30 seconds unsupported ( ) 1 needs several tries to stand 30 seconds unsupported ( ) 0 unable to stand 30 seconds unsupported If a subject is able to stand 2 minutes unsupported, score full points for sitting unsupported. Proceed to item #4.
<b>03</b>	<b>SITTING WITH BACK UNSUPPORTED BUT FEET SUPPORTED ON FLOOR OR ON A STOOL</b> <b>INSTRUCTIONS: Please sit with arms folded for 2 minutes.</b>  ( ) 4 able to sit safely and securely for 2 minutes ( ) 3 able to sit 2 minutes under supervision ( ) 2 able to sit 30 seconds ( ) 1 able to sit 10 seconds ( ) 0 unable to sit without support 10 seconds
<b>04</b>	<b>STANDING TO SITTING</b> <b>INSTRUCTIONS: Please sit down.</b>  ( ) 4 sits safely with minimal use of hands ( ) 3 controls descent by using hands ( ) 2 uses back of legs against chair to control descent ( ) 1 sits independently but has uncontrolled descent ( ) 0 needs assist to sit
<b>05</b>	<b>TRANSFERS</b> <b>INSTRUCTIONS: Arrange chair(s) for pivot transfer. Ask subject to transfer one way toward a seat with armrests and one way toward a seat without armrests. You may use two chairs (one with and one without armrests) or a bed and a chair.</b>  ( ) 4 able to transfer safely with minor use of hands ( ) 3 able to transfer safely definite need of hands ( ) 2 able to transfer with verbal cuing and/or supervision ( ) 1 needs one person to assist ( ) 0 needs two people to assist or supervise to be safe

06	<p><b>STANDING UNSUPPORTED WITH EYES CLOSED</b>  <b>INSTRUCTIONS: Please close your eyes and stand still for 10 seconds.</b></p> <p>( ) 4 able to stand 10 seconds safely  ( ) 3 able to stand 10 seconds with supervision  ( ) 2 able to stand 3 seconds  ( ) 1 unable to keep eyes closed 3 seconds but stays safely  ( ) 0 needs help to keep from falling</p>
07	<p><b>STANDING UNSUPPORTED WITH FEET TOGETHER</b>  <b>INSTRUCTIONS: Place your feet together and stand without holding on.</b></p> <p>( ) 4 able to place feet together independently and stand 1 minute safely  ( ) 3 able to place feet together independently and stand 1 minute with supervision  ( ) 2 able to place feet together independently but unable to hold for 30 seconds  ( ) 1 needs help to attain position but able to stand 15 seconds feet together  ( ) 0 needs help to attain position and unable to hold for 15 seconds</p>
08	<p><b>REACHING FORWARD WITH OUTSTRETCHED ARM WHILE STANDING</b>  <b>INSTRUCTIONS: Lift arm to 90 degrees. Stretch out your fingers and reach forward as far as you can. (Examiner places a ruler at the end of fingertips when arm is at 90 degrees. Fingers should not touch the ruler while reaching forward. The recorded measure is the distance forward that the fingers reach while the subject is in the most forward lean position. When possible, ask subject to use both arms when reaching to avoid rotation of the trunk.)</b></p> <p>( ) 4 can reach forward confidently 25 cm (10 inches)  ( ) 3 can reach forward 12 cm (5 inches)  ( ) 2 can reach forward 5 cm (2 inches)  ( ) 1 reaches forward but needs supervision  ( ) 0 loses balance while trying/requires external support</p>
09	<p><b>PICK UP OBJECT FROM THE FLOOR FROM A STANDING POSITION</b>  <b>INSTRUCTIONS: Pick up the shoe/slipper, which is in front of your feet.</b></p> <p>( ) 4 able to pick up slipper safely and easily  ( ) 3 able to pick up slipper but needs supervision  ( ) 2 unable to pick up but reaches 2-5 cm(1-2 inches) from slipper and keeps balance independently  ( ) 1 unable to pick up and needs supervision while trying  ( ) 0 unable to try/needs assist to keep from losing balance or falling</p>
10	<p><b>TURNING TO LOOK BEHIND OVER LEFT AND RIGHT SHOULDERS WHILE STANDING</b>  <b>INSTRUCTIONS: Turn to look directly behind you over toward the left shoulder. Repeat to the right. (Examiner may pick an object to look at directly behind the subject to encourage a better twist turn.)</b></p> <p>( ) 4 looks behind from both sides and weight shifts well  ( ) 3 looks behind one side only other side shows less weight shift  ( ) 2 turns sideways only but maintains balance  ( ) 1 needs supervision when turning  ( ) 0 needs assist to keep from losing balance or falling</p>

11	<p><b>TURN 360 DEGREES</b>  <b>INSTRUCTIONS:</b> Turn completely around in a full circle. Pause. Then turn a full circle in the other direction.</p> <p>( ) 4 able to turn 360 degrees safely in 4 seconds or less  ( ) 3 able to turn 360 degrees safely one side only 4 seconds or less  ( ) 2 able to turn 360 degrees safely but slowly  ( ) 1 needs close supervision or verbal cuing  ( ) 0 needs assistance while turning</p>
12	<p><b>PLACE ALTERNATE FOOT ON STEP OR STOOL WHILE STANDING UNSUPPORTED</b>  <b>INSTRUCTIONS:</b> Place each foot alternately on the step/stool. Continue until each foot has touched the step/stool four times.</p> <p>( ) 4 able to stand independently and safely and complete 8 steps in 20 seconds  ( ) 3 able to stand independently and complete 8 steps in &gt; 20 seconds  ( ) 2 able to complete 4 steps without aid with supervision  ( ) 1 able to complete &gt; 2 steps needs minimal assist  ( ) 0 needs assistance to keep from falling/unable to try</p>
13	<p><b>STANDING UNSUPPORTED ONE FOOT IN FRONT</b>  <b>INSTRUCTIONS: (DEMONSTRATE TO SUBJECT)</b> Place one foot directly in front of the other. If you feel that you cannot place your foot directly in front, try to step far enough ahead that the heel of your forward foot is ahead of the toes of the other foot. (To score 3 points, the length of the step should exceed the length of the other foot and the width of the stance should approximate the subject's normal stride width.)</p> <p>( ) 4 able to place foot tandem independently and hold 30 seconds  ( ) 3 able to place foot ahead independently and hold 30 seconds  ( ) 2 able to take small step independently and hold 30 seconds  ( ) 1 needs help to step but can hold 15 seconds  ( ) 0 loses balance while stepping or standing</p>
14	<p><b>STANDING ON ONE LEG</b>  <b>INSTRUCTIONS:</b> Stand on one leg as long as you can without holding on.</p> <p>( ) 4 able to lift leg independently and hold &gt; 10 seconds  ( ) 3 able to lift leg independently and hold 5-10 seconds  ( ) 2 able to lift leg independently and hold L 3 seconds  ( ) 1 tries to lift leg unable to hold 3 seconds but remains standing independently.  ( ) 0 unable to try of needs assist to prevent fall</p>

**Appendix 8.36.** Description of the Timed Up and Go (TUG) test.

The TUG is a clinical test that measures, in seconds, the time needed by an individual to stand up from a standard arm chair with arms, walk a distance of 3 metres, turn, walk back to the chair and sit down again (Podsiadlo and Richardson, 1991). In the current study, the height of the chairs with arms were between 45.5 and 47 cm, and the height of arm chairs between 65 and 67.5 cm. Patients using a walking aid, performed the test using their walking aid. However, they used the same assistive device each time they performed the test to be able to compare scores between the study's assessments. The starting and final position of the test was with the patients' back against the chair, the arms resting on the chair's arms, feet behind the tape marker, and the walking aid at hand (Podsiadlo and Richardson, 1991). Time to complete the test was measured to the nearest 100th of a second (Steffen and Seney, 2008). The end of the walking path was marked with a small red cone. The patients had to turn around the cone and not turning on the spot. No instructions were given during the test performance, except the initial order 'go'. On a data sheet the time to complete the test was recorded, and qualitative aspects of walking (such as freezing, no arms swinging) were ticked.

The researcher demonstrated first the test to the participants. Patients were advised to have their comfortable walking speed during the test. The patients had one practice trial, which was not included in the score, to become familiar with the test (Podsiadlo and Richardson, 1991). Although in many previous studies in PD, the average time of two (Brusse et al., 2005) or three (Dibble et al., 2008) trials was calculated and used in the analysis; in the current study, the patients had one practice trial and one timed trial for the test (Podsiadlo and Richardson, 1991). Despite the fact that the EPDA proposes to perform the test both during the on- and off-state to identify PD patients at high risk of falling (Keus et al., 2013), the assessments in the current RCT were performed only during the on-state for safety reasons.

**Appendix 8.37. Timed Up and Go (TUG) test form (Greek version).****Δοκιμασία 'σήκω και ξεκίνα' (TUG)**

Όνομα: \_\_\_\_\_

Ημερομηνία: \_\_\_\_\_

Βοήθημα βάδισης : \_\_\_\_\_

Χρόνος TUG τεστ σε δευτερόλεπτα : \_\_\_\_\_

Αν ισχύει κάτι από τα παρακάτω, παρακαλώ σημειώστε με (X):

- ☐ Πάγωμα
- ☐ Αργά βήματα στην αρχή
- ☐ Μικρός διασκελισμός
- ☐ Έλλειψη ισορροπίας
- ☐ Ελλιπής ή μικρή αιώρηση των χεριών
- ☐ Μη σωστή χρήση βοηθήματος βάδισης
- ☐ Άλλο: .....



**Appendix 8.38. Timed Up and Go (TUG) test form (English version).****Timed Up and Go Test (TUG)**

Name: \_\_\_\_\_

Date: \_\_\_\_\_

Type of walking aid : \_\_\_\_\_

TUG time in seconds : \_\_\_\_\_

If any of the following is true, please tick (X):

- ☐ Freezing
- ☐ Slow steps in the beginning
- ☐ Small stride
- ☐ Lack of balance
- ☐ Reduced or not arms swings
- ☐ Inappropriate use of the walking aid
- ☐ Other: .....

**Appendix 8.39.** Description of the Falls Efficacy Scale International (FES-I)

The FES-I is a self-report instrument, which includes 16 items about common activities that are scored on a four point ordinal scale from one (not at all concerned) to four (very concerned). The total score ranges from 16 to 64. Higher scores are associated with higher FOF. Scores more than 23 indicate high concern about falling (Yardley et al., 2005).

**Appendix 8.40.** Falls Efficacy Scale International (FES-I) (Greek version)**ΔΙΕΘΝΗΣ ΚΛΙΜΑΚΑ ΑΝΥΣΗΧΙΑΣ ΠΤΩΣΕΩΝ (FES-I)**

Όνομα: .....

Ημερομηνία: .....

Θα θέλαμε να σας κάνουμε κάποιες ερωτήσεις σχετικά με το πόσο σας απασχολεί η πιθανότητα να πέσετε. Για κάθε μία από τις παρακάτω δραστηριότητες, παρακαλώ σημειώστε την απάντηση που σας εκφράζει καλύτερα, για το πόσο δηλαδή σας απασχολεί το γεγονός μιας πιθανής πτώσης. Παρακαλώ να απαντήσετε βάσει του τρόπου με τον οποίο συνήθως κάνετε την κάθε δραστηριότητα. Αν την περίοδο αυτή δεν κάνετε κάποια από τις παρακάτω δραστηριότητες (αν για παράδειγμα κάποιος άλλος ψωνίζει για εσάς), παρακαλώ απαντήστε δείχνοντάς μας πόσο θα σας απασχολούσε η πιθανότητα μιας πτώσης αν κάνατε αυτήν τη δραστηριότητα.

		Δε με απασχολεί καθόλου 1	Με απασχολεί λίγο 2	Με απασχολεί αρκετά 3	Με απασχολεί πολύ 4
01	Όταν καθαρίζω το σπίτι (π.χ. σφουγγάρισμα, σκούπισμα ή ξεσκόνισμα)				
02	Όταν ντύνομαι ή γδύνομαι				
03	Όταν ετοιμάζω ένα απλό φαγητό				
04	Όταν κάνω μπάνιο ή ντους				
05	Όταν πηγαίνω για τα καθημερινά ψώνια				
06	Όταν κάθομαι ή σηκώνομαι από μια καρέκλα				

		Δε με απασχολεί καθόλου 1	Με απασχολεί λίγο 2	Με απασχολεί αρκετά 3	Με απασχολεί πολύ 4
07	Όταν ανεβαίνω ή κατεβαίνω σκάλες				
08	Όταν κάνω βόλτα στην γειτονιά				
09	Όταν προσπαθώ να φτάσω κάτι που βρίσκεται ψηλά (π.χ. ράφι) ή στο έδαφος				
10	Όταν πάω να προλάβω το τηλέφωνο				
11	Όταν περπατάω σε μία επιφάνεια που γλιστράει (π.χ. με πάγο ή βρεγμένη)				
12	Όταν πάω για επίσκεψη σε ένα φίλο ή συγγενή				
13	Όταν περπατάω κάπου που έχει πολύ κόσμο π.χ. στη λαϊκή				
14	Όταν περπατάω πάνω σε ανώμαλο έδαφος (π.χ. πέτρες, κακοσυντηρημένο πεζοδρόμιο)				
15	Όταν περπατάω σε ανηφόρα ή κατηφόρα				
16	Όταν πηγαίνω σε μία κοινωνική εκδήλωση (π.χ. εκκλησία, οικογενειακή συγκέντρωση, καφενείο, ΚΑΠΗ)				

Σας ευχαριστούμε για την συμμετοχή σας. Ελέγξτε ότι έχετε απαντήσει όλες τις ερωτήσεις.

Συνολικό σκορ: .....

**Appendix 8.41. Falls Efficacy Scale International (FES-I) (English version)****FALLS EFICACY SCALE-INTERNATIONAL (FES-I)**

Name: .....

Date: .....

Now we would like to ask some questions about how concerned you are about the possibility of falling. For each of the following activities, please circle the opinion closest to your own to show how concerned you are that you might fall if you did this activity. Please reply thinking about how you usually do the activity. If you currently don't do the activity (e.g. if someone does your shopping for you), please answer to show whether you think you would be concerned about falling if you did the activity.

		<b>Not at all concerned 1</b>	<b>Somewhat concerned 2</b>	<b>Fairly concerned 3</b>	<b>Very concerned 4</b>
01	Cleaning the house (e.g. sweep, vacuum or dust)				
02	Getting dressed or undressed				
03	Preparing simple meals				
04	Taking a bath or shower				
05	Going to the shop				
06	Getting in or out of a chair				
07	Going up or down stairs.				
08	Walking around in the neighborhood				

		<b>Not at all concerned 1</b>	<b>Somewhat concerned 2</b>	<b>Fairly concerned 3</b>	<b>Very concerned 4</b>
09	Reaching for something above your head or on the ground				
10	Going to answer the telephone before it stops ringing				
11	Walking on a slippery surface (e.g. wet or icy)				
12	Visiting a friend or relative				
13	Walking in a place with crowds				
14	Walking on an uneven surface (e.g. rocky ground, poorly maintained pavement)				
15	Walking up or down a slope				
16	Going out to a social event (e.g. religious service, family gathering or club meeting)				

**Please check you have answered all the questions.**

**Total score: .....**

**Appendix 8.42.** Completion of the falls diary (FD) and falls questionnaire (FQ).

Both the FD and FQ were self-report tools, completed by the participants. The patients had to circle the day(s) they experienced a fall, and write the number of falls in the appropriate date box of the FD. The fall definition was written in each FD. In case they had a fall, the FQ had to be completed (one FQ for each fall). The FD and the FQ were parts of the booklets (supplements 4-7) given to the participants during the intervention and follow-up period. Extra FQs were given to participants, if needed.

Concerning the baseline assessment, the participants were asked to record the falls they experienced during the last two months. The assistant physiotherapist provided assistance for the completion of questionnaires, if needed.

## Appendix 8.43. Falls Diary (FD) (Greek version)

**ΗΜΕΡΟΛΟΓΙΟ ΠΤΩΣΕΩΝ (FD)**

Όνομα: .....

Ημερομηνία: .....

Στο παρακάτω ημερολόγιο, κυκλώστε την ημερομηνία που είχατε κάποια πτώση. Σε περίπτωση που είχατε τουλάχιστον 2 πτώσεις την ίδια ημέρα, παρακαλώ σημειώστε και τον αριθμό πτώσεων στο αντίστοιχο κουτί. Για κάθε πτώση, συμπληρώνετε και ένα «Ερωτηματολόγιο Πτώσης».

**Ορισμός πτώσης:** «Η πτώση είναι ένα ξαφνικό, απροσδόκητο γεγονός που έχει ως αποτέλεσμα να ακουμπήσετε ή να πέσετε χωρίς την θέλησή σας στο έδαφος ή σε κάποιο άλλο χαμηλότερο επίπεδο»

ΜΑΪΟΣ 2015						
Δ	Τ	Τ	Π	Π	Σ	Κ
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	31



**Appendix 8.44. Falls Diary (FD) (English version)**

**FALLS DIARY (FD)**

**Name:** .....

**Date:** .....

In the following calendar, circle the date you have a fall. If you have at least 2 falls on the same day, please write the number of falls in the date box. For each fall, you are requested to complete a "Fall Questionnaire".

**Fall definition:** "Fall is a sudden, unexpected event that results in coming to rest unintentionally on the ground or at some other lower level"

MAY 2015						
M	T	W	T	F	S	S
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	31

## Appendix 8.45. Falls Questionnaire (FQ) (Greek version)

## ΕΡΩΤΗΜΑΤΟΛΟΓΙΟ ΠΤΩΣΗΣ (FQ)

Όνομα: .....

Ημερομηνία: .....

Αν σημειώσατε μια πτώση στο «ημερολόγιο πτώσεων», παρακαλώ συμπληρώστε το παρακάτω ερωτηματολόγιο. Αν δεν θυμάστε κάτι, παρακαλώ αφήστε κενή την απάντηση.

01	Ημερομηνία πτώσης	
02	Ώρα πτώσης	
03	Τόπος πτώσης	
04	Μπορείτε να περιγράψετε τι προκάλεσε τη πτώση;	
05	Κατεύθυνση πτώσης	<input type="checkbox"/> μπροστά <input type="checkbox"/> πίσω <input type="checkbox"/> πλάγια <input type="checkbox"/> κατευθείαν κάτω
06	Πόσο καλά λειτουργούσε η φαρμακευτική σας αγωγή για το Πάρκινσον την ώρα της πτώσης;	<input type="checkbox"/> λειτουργούσε καλά <input type="checkbox"/> μέτρια <input type="checkbox"/> δεν λειτουργούσε <input type="checkbox"/> δεν έπαιρνα φαρμακευτική αγωγή

07	Είχατε κάποιο πάγωμα την ώρα της πτώσης (πχ νιώσατε ότι τα πόδια σα ήταν κολλημένα στο έδαφος);	<input type="checkbox"/> Ναι <input type="checkbox"/> Όχι
08	Χρησιμοποιούσατε κάποιο βοήθημα βάδισης όταν πέσατε;	<input type="checkbox"/> Ναι <input type="checkbox"/> Όχι
09	Είχατε κάποιον τραυματισμό εξαιτίας της πτώσης;	<input type="checkbox"/> Ναι <input type="checkbox"/> Όχι  Αν ναι, προσδιορίστε:
10	Χρειαστήκατε ιατρική βοήθεια;	<input type="checkbox"/> Ναι <input type="checkbox"/> Όχι
11	Αν απαντήσατε ναι στη προηγούμενη ερώτηση, προσδιορίστε.	<input type="checkbox"/> Νοσοκομείο <input type="checkbox"/> Ιδιωτικό ιατρείο <input type="checkbox"/> Άλλο: .....
12	Αν νοσηλευτήκατε σε νοσοκομείο, αναφέρατε πόσα βράδια παραμείνατε εκεί.	

**Appendix 8.46. Falls Questionnaire (FQ) (English version)****FALLS QUESTIONNAIRE (FQ)**

Name:.....

Date:.....

**If you ticked a fall in the “falls diary”, please complete the following questionnaire. If you do not remember any answer, please leave it blank.**

01	Date of fall	
02	Time of fall	
03	Location of fall	
04	Can you describe what caused the fall?	
05	Direction of fall	<input type="checkbox"/> forwards <input type="checkbox"/> backwards <input type="checkbox"/> sideways <input type="checkbox"/> straight down
06	How well was your medication working at the time of fall?	<input type="checkbox"/> working well <input type="checkbox"/> working moderate <input type="checkbox"/> not working <input type="checkbox"/> not under medication treatment

07	Did you experience any freezing at the time of the fall (i.e. did you feel like your feet were stuck to the floor)?	<input type="checkbox"/> Yes <input type="checkbox"/> No
08	Were you using a walking aid when you fell?	<input type="checkbox"/> Yes <input type="checkbox"/> No
09	Did you suffer any injuries?	<input type="checkbox"/> Yes <input type="checkbox"/> No If 'yes', indicate:
10	Did you seek medication attention?	<input type="checkbox"/> Yes <input type="checkbox"/> No
11	If you answered yes to the previous question, please indicate where	<input type="checkbox"/> Hospital <input type="checkbox"/> Medical office <input type="checkbox"/> Other:
12	If you admitted to the hospital indicate the number of nights you stayed there.	

**Appendix 8.47. Protocol for the 2 Minute Walk Test (2MWT).***Equipment*

The equipment of the 2MWT included: a stopwatch, two small cones to mark the turnaround points, a chair that could be easily moved along the walking course, an electronic sphygmomanometre (microlife BP A3 PC), a pulse oximetre (NONIN 9570), one laminating sheet with the Borg scale. The ten-point Borg scale was selected, as it more commonly used in Greece; and it is both valid and reliable (Kendrick et al., 2000).

*Assessment parameters*

The 2MWT, assessed the 2MWD; and major cardiorespiratory parameters including the heart rate (HR), oxygen saturation (SpO<sub>2</sub>), systolic blood pressure (SBP), diastolic blood pressure (DBP), dyspnoea and fatigue of lower limbs (ATS, 2002). The HR and SpO<sub>2</sub> were assessed by the pulse oximetre; the SBP and DBP by the sphygmomanometre; and the dyspnoea and fatigue of lower limbs by the 10-point Borg Scale. Four measures were performed in each trial: before the start of the test, at the first minute, at the end of the test, and two minutes after the test end. As it is not established whether the 2MWT can capture data of aerobic endurance, due to its limited time compared to the 6MWT (Bohannon et al., 2015), and as this was not the main outcome measure of the study; only the 2MWD was included in the analysis.

*Assessors' responsibilities*

Two assessors participated in the 2MWT: the researcher and an assistant physiotherapist. The researcher measured the cardiorespiratory parameters before and after the test, demonstrated the test, gave all the verbal instructions and supervised the participant. The assistant physiotherapist recorded the cardiorespiratory parameters and the number of turns during the test on the 2MWT sheet. Then, the 2MWD was calculated and recorded, based on the number of turns and additional distance covered. The distance covered around the cones was estimated at 0.50 metres. As there were two trials, only the highest 2MWD was used for the data analysis (ATS, 2002).

*Protocol*

In the current study, the 2MWT was conducted following a modified standardised procedure, based on the ATS guidelines for the 6MWT (ATS, 2002). The absolute contraindications and the reasons for immediately stopping the test, were strictly followed. Few modifications were made due to: the lack of space to perform the test; restricted time of the 2MWT (2 minutes) compared to the 6MWT, and assessment session; and motor features of PD. These modifications are listed as follows:

- Although the perfect walking path is 30-metre long (ATS, 2002); in the current study, the test was performed in a 12-metre walking path, and at least 2.5 metres wide, due to the lack of space. The length of the walking path was marked every two metres with a coloured tape. However, a shorter corridor than 30 metres requires more time for the patients to reverse directions, reducing the covered distance (ATS, 2002).
- As the total test time was only two minutes, only four verbal instructions were given during the test: 1) 'Go' to start the test; 2) when one minute elapsed, the participants were told: 'You are doing well; you have one minute left.' (Bohannon et al, 2015). 3) When the timer was 15 seconds from completion: 'In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you.' 4) 'Stop' at the end of the test (ATS, 2002).
- In the current study, two trials were performed. The subjects were given a 10-minute rest before the two trials to avoid fatigue (Light et al, 1997; Pin, 2014). Due to the restricted time of assessment, it was impossible to leave the patients at least one hour to rest (ATS, 2002).
- The subjects were instructed to turn wide around the cones in a half circle and extend the width of the hallway. This type of turn minimises the complications of freezing and instability. No cues were used, except the tapes and the cones on the floor (Light et al., 1997).

The procedure of the test was simple. The participants were instructed to walk on the flat level surface from end to end of the line, turn around the cones, and to cover as much distance as possible. Running or jogging were not allowed during the test. They were also

told not to worry if they had to slow down or rest; but, that if they stopped they should start walk again as soon as they feel ready to do so. Walking aids were used by some patients, but were kept consistent from test to test.



## Appendix 8.48. 2MWT sheet (Greek version).

## ΔΟΚΙΜΑΣΙΑ 2 ΛΕΠΤΩΝ ΒΑΔΙΣΗΣ

ΟΝΟΜΑ:
ΗΜΕΡΟΜΗΝΙΑ:

Κάθε φορά που ολοκληρώνεται μισός γύρος από τον ασκούμενο να κυκλώνεται ένα νούμερο. **ΠΡΟΣΟΧΗ:** Κάθε δοκιμασία θα διακόπτεται εάν ο ασκούμενος αισθανθεί: πόνο στο στήθος, μη ανεκτή δύσπνοια, κράμπα στα κάτω άκρα, ζάλη, έντονη εφίδρωση, χλωμάδα στο πρόσωπο.

ΜΙΣΟΣ ΓΥΡΟΣ	1	2	3	4	5	6	7	8	9	10	11
	12	13	14	15	16	17	18	19	20	21	22
	23	24	25	26	27	28	29	30	31	32	33
ΣΤΑΣΕΙΣ	1	2	3	4	5	6	7	8	9	10	11
Επιπλέον απόσταση (μέτρα)											
Συνολικά Διανυόμενη Απόσταση											

Τερμάτισε τη δοκιμασία (βάλτε σε κύκλο): ΜΕ / ΧΩΡΙΣ ΔΙΑΚΟΠΗ

Αν ΜΕ ΔΙΚΑΚΟΠΗ, ποιος ο ΛΟΓΟΣ:

	ΚΟΡ.	Κ.Σ.	ΔΥΣΠΝΟΙΑ	ΚΟΠΩΣΗ	Δ.Α.Π.	Σ.Α.Π.
ΠΡΙΝ						
1						
2						
2 ΑΠΟΚ						

## Appendix 8.49. 2MWT sheet (English version).

## 2 MINUTE WALK TEST

NAME:
DATE:

When a half circle is completed by the trainee, please circle a number.

**ATTENTION: Reasons for immediately stopping a 2MWT include the following: (1) chest pain, (2) intolerable dyspnea, (3) leg cramps, (4) staggering, (5) diaphoresis, and (6) pale or ashen appearance.**

HALF ROUND	1	2	3	4	5	6	7	8	9	10	11
	12	13	14	15	16	17	18	19	20	21	22
	23	24	25	26	27	28	29	30	31	32	33
STOPS	1	2	3	4	5	6	7	8	9	10	11
Additional walking distance (metres):											
Total walking distance:											

The patient completed successfully the test (circle): Yes / No

If 'No', state the reason:

	SAT	HR	DYSPNOEA	FATIGUE	DBP	SBP
BEFORE						
1 MIN						
2 MIN						
2 MIN AFTER						

Appendix 8.50. Borg scale (Greek version)

## ΚΛΙΜΑΚΑ BORG

<b>0</b>	<b>Καμία Αίσθηση Δυσκολίας</b>
<b>0,5</b>	<b>Πάρα πού ελαφριά (μόλις αισθητή)</b>
<b>1</b>	<b>Πολύ Ελαφριά</b>
<b>2</b>	<b>Ελαφριά</b>
<b>3</b>	<b>Μέτρια</b>
<b>4</b>	<b>Λίγο Δύσκολη</b>
<b>5</b>	<b>Δύσκολη (βαριά)</b>
<b>6</b>	
<b>7</b>	<b>Πολύ Δύσκολη</b>
<b>8</b>	
<b>9</b>	
<b>10</b>	<b>Πάρα πολύ δύσκολη (μέγιστη)</b>

Appendix 8.51. Borg scale (English version).

## BORG SCALE

<b>0</b>	<b>Nothing at all</b>
<b>0,5</b>	<b>Very, very slight (just noticeable)</b>
<b>1</b>	<b>Very slight</b>
<b>2</b>	<b>Slight (light)</b>
<b>3</b>	<b>Moderate</b>
<b>4</b>	<b>Somewhat severe</b>
<b>5</b>	<b>Severe (heavy)</b>
<b>6</b>	
<b>7</b>	<b>Very severe</b>
<b>8</b>	
<b>9</b>	
<b>10</b>	<b>Very, very severe (maximal)</b>

**Appendix 8.52. Protocol for the spirometry.**

The guidelines of the ATS and the European Respiratory Society were followed for the spirometry (Miller et al., 2005). Before the test, the patients were checked for absolute and relevant contraindications. Two types of measurement were performed: a forced and a slow spirometry. Firstly, the test was explained and demonstrated to participants (García-Río et al, 2013; Miller et al., 2005). Then, details of the patients' gender, age, height, weight, and ethnical background were entered to the device. The age was expressed in years; height in centimetres; and weight in kilos. Afterwards, the patients performed the spirometry tests.

Spirometry was performed with the subjects in sitting position. The chair was with arms and without wheels for safety reasons (Miller et al., 2005). The head was held in a neutral position; both feet were on the ground and the elbows on armchairs (García-Río et al., 2013). During the whole manoeuvre, lips were sealed around the mouthpiece; and nose clip was used to prevent possible air leaks on breathing through the nose. (García-Río et al, 2013; Miller et al, 2005). Thus, inspiration and expiration was performed through the mouthpiece. The slow spirometry was performed first, because forced spirometry manoeuvres may cause muscular fatigue (Miller et al, 2005). Three manoeuvres were performed for the forced and slow spirometry, separated by a small rest period of one minute (García-Río et al., 2013).

In the slow spirometry, the patients were asked to breathe calmly (tidal breathing) through the mouthpiece, at least three breaths were performed (to verify the functional residual capacity-FRC- is stable); then, to inspire until the total lung capacity (TLC), and exhale up to residual volume (RV). In the forced spirometry, the patients were asked to inhale through the mouthpiece to reach their TLC from their FRC; then to blow hard and fast through the mouthpiece, and prolong the expiration without stopping until told to do it (García-Río et al., 2013; Miller et al., 2005). Throughout the manoeuvres, the researcher guided the

participants, using appropriate body language and phrases: “take air” (πάρε αέρα), and “blow” (φύσα) (Miller et al., 2005).

The best performed manoeuvre was selected automatically by the spirometre. The values of measured variables were recorded in L or L/sec, and in percentages of the predicted normal values. The results of the spirometry test for each patient was stored on the computer and printed. The following respiratory variables were included in the analysis section: forced expiratory volume in the first second (FEV<sub>1</sub>), forced vital capacity (FVC), FEV<sub>1</sub>/FVC ratio, inspiratory vital capacity (IVC). FEV<sub>1</sub>, FVC and FEV<sub>1</sub>/FVC were recorded during the forced spirometry; whereas IVC during the slow spirometry.

## Appendix 8.53. Satisfaction Questionnaire (SQ) (Greek version)

## ΕΡΩΤΗΜΑΤΟΛΟΓΙΟ ΣΧΕΤΙΚΑ ΜΕ ΤΟ ΠΡΟΓΡΑΜΜΑ ΑΣΚΗΣΗΣ (SQ)

Το παρόν ερωτηματολόγιο αφορά τη γνώμη σας σχετικά με το ομαδικό πρόγραμμα άσκησης που παρακολουθήσετε. Η συμπλήρωση του ερωτηματολογίου και των ερωτήσεων του είναι προαιρετική. Παρακαλείσθε ανεξάρτητα από το αν συμπληρώσατε το ερωτηματολόγιο, να το τοποθετήσετε στον φάκελο που σας δόθηκε. Κλείστε καλά τον φάκελο και φέρτε το πίσω στο επόμενο ραντεβού.

01	Πόσο εύκολο/δύσκολο ήταν το πρόγραμμα άσκησης;
02	Παρατηρήσατε θετικά αποτελέσματα από τη συμμετοχή σας στο πρόγραμμα; Αν ναι, σημειώσατε.
03	Παρατηρήσατε αρνητικά αποτελέσματα από τη συμμετοχή σας στο πρόγραμμα; Αν ναι σημειώσατε.
04	Τι σας άρεσε περισσότερο στο πρόγραμμα;

05	Τι σας άρεσε λιγότερο στο πρόγραμμα;
06	Τι θα αλλάζατε στο πρόγραμμα άσκησης; Έχετε κάποιες ιδέες να προτείνετε;
07	Τι σας ώθησε να συμμετάσχετε στο πρόγραμμα;
08	Τι σας ώθησε να ολοκληρώσετε το πρόγραμμα;
09	Θα θέλατε να προσθέσετε κάτι άλλο;

**Σας ευχαριστούμε για τον χρόνο σας!**



**Appendix 8.54. Satisfaction Questionnaire (SQ) (English version)****SATISFACTION QUESTIONNAIRE FOR THE EXERCISE (SQ)**

**This questionnaire is relevant to your personal opinion about the group-based exercise programme you attended. The completion of the questionnaire and its questions is optional. Regardless you complete or not the questionnaire, you are requested it to place into the envelope given to you. Close the envelope and bring it back to us in you next appointment.**

01	How easy/hard was the programme?
02	Have you noticed any positive effects from doing the programme? If yes, please report them.
03	Have you noticed any negative effects from doing the programme? If yes, please report them.
04	What did you like more about the programme?

05	What did you like less about the programme?
06	What would you like to change in the programme? Any ideas to propose?
07	What motivated you to participate to the programme?
08	What motivated you to complete the programme?
09	Do you have anything else you would like to add?

**Thank you for your time!**

**Appendix 8.55.** Attendance form (AF)- group programme.

<b>MUNICIPALITY:</b>	<b>Session 8</b>	<b>Education</b>						
		<b>Exercise</b>						
	<b>Session 7</b>	<b>Exercise</b>						
	<b>Session 6</b>	<b>Education</b>						
		<b>Exercise</b>						
	<b>Session 5</b>	<b>Exercise</b>						
	<b>Session 4</b>	<b>Education</b>						
		<b>Exercise</b>						
	<b>Session 3</b>	<b>Exercise</b>						
	<b>Session 2</b>	<b>Education</b>						
		<b>Exercise</b>						
	<b>Session 1</b>	<b>Exercise</b>						
	<b>Name</b>							
<b>Code</b>								

**Appendix 8.56.** Attendance form (AF)- individualised programme.

Code	Name	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8

**Appendix 8.57.** Analytical description of the respiratory exercises.Diaphragmatic breathing

The diaphragmatic breathing was performed for one minute. Full, deep breaths allow the diaphragm to lower and the lungs to expand deeply, ensuring that more oxygen is taken in with each breath. The technique involves taking a deep inspiration through nose with the mouth closed. The exhalation is slowly lasting for four to six seconds through pursed lips held in a whistling or kissing position. The technique starts with exhalation (Christara-Papadopoulou, 2009).

Breathing-enhanced upper extremity exercises

Similarly to the study by Mutluay et al. (2007) in Multiple Sclerosis, breathing-enhanced upper extremity exercises were included in the current project. One set of ten repetitions was performed. The exercise included two parts: inspiration while abducting horizontally both shoulders; expiration while returning the arms to the initial position. The technique started with exhalation. Furthermore, the patients were instructed to inspire through the nose and expire through the mouth with pursed-lip breathing. At the end of inspiratory, a sniff and an end-inspiratory hold were added gradually. One rapid nasal sniff at the end of inspiration may further augment collateral ventilation, because even after a full inspiration, the individual does not reach the TLC. Then, an end-inspiratory hold was followed, to boost collateral ventilation and distribute air more evenly between lung segments. The duration of the hold breath was three to four seconds (Christara- Papadopoulou, 2009).

IMT using a Threshold IMT device

The IMT was performed using an inspiratory muscle trainer (Threshold IMT). Threshold IMT is a hand-held, spring-loaded device designed to strengthen inspiratory respiratory muscles. The device incorporates a flow-independent, one-way valve to ensure consistent resistance during inhalation. The patients inhaled and exhaled through the device. The

participants had to wear the nose clips during the exercise. The mouthpiece had been sterilised prior the use for hygiene reasons (Christara- Papadopoulou, 2009).

Previous effective trials examining the effectiveness of IMT in neurodegenerative disorders had either specific duration of treatment, measured in minutes (Inzelberg et al., 2005); or specific sets and repetitions (Klefbeck and Hamrah Nedjad, 2003; Fry et al., 2007). The training load and the progression of exercise were expressed based on the MIP (Klefbeck and Hamrah Nedjad, 2003). Furthermore, the total training length varied from four to 12 weeks; and the exercise frequency from five to seven days a week (Reyes et al., 2013). In the current study, due to the total duration of each session, it was decided to perform two sets of ten repetitions (Klefbeck and Hamrah Nedjad, 2003). However, due to the lack of MIP device, the subjects started breathing at a low load (11cm H<sub>2</sub>O). There was an increase in the training load by 2 cm H<sub>2</sub>O every week.

## Appendix 8.58. Signed consent for the photo shoot (Greek version).

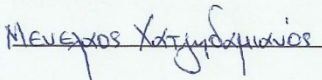
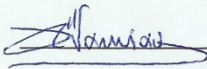
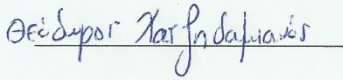

**ΕΝΤΥΠΟ ΣΥΓΚΑΤΑΘΕΣΗΣ ΓΙΑ ΤΗΝ ΦΩΤΟΓΡΑΦΙΣΗ**

‘Η αποτελεσματικότητα ενός ομαδικού προγράμματος άσκησης και εκπαίδευσης για την βελτίωση της κατάθλιψης, του άγχους, της ποιότητας ζωής και της πρόληψης των πτώσεων σε ελληνικό πληθυσμό με τη νόσο του Πάρκινσον.’

Επιβεβαιώνω ότι έχω κατανοήσει:

- Το σκοπό της παρούσας έρευνας και του παρόντος εγχειριδίου.
- Ότι η συμμετοχή μου για την φωτογράφιση είναι εθελοντική.
- Ότι οι φωτογραφίες θα χρησιμοποιηθούν για το εγχειρίδιο με τίτλο ‘Εγχειρίδιο ατομικής άσκησης στο σπίτι’ και για την διπλωματική εργασία του κ. Θεόδωρου Χατζηδαμανίου, και όχι για εμπορικούς σκοπούς.
- Ότι οι φωτογραφίες θα αποκρύπτουν τα χαρακτηριστικά του προσώπου μου.
- Η ανωνυμία μου είναι εγγυημένη

Δέχομαι να είμαι το μοντέλο της φωτογράφισης.

 Όνομα συμμετέχοντα	18/12/2014 Ημερομηνία	 Υπογραφή
 Όνομα ερευνητή	18/12/2014 Ημερομηνία	 Υπογραφή

## Appendix 8.59. Signed consent for the photo shoot (English version).

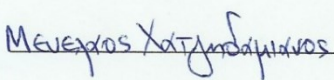
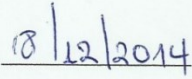
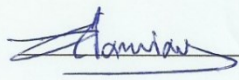
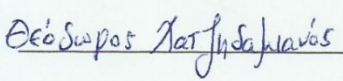
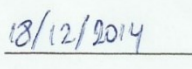

**CONSENT FORM FOR THE PHOTO SHOOT**

‘The effectiveness of a group exercise programme on improving anxiety, depression, quality of life and prevention of falls in Greek elderly population suffering from Parkinson’s disease.’

I confirm that I have understood:

- the aim of the current research and booklet.
- that my participation for the photo shoot is voluntary.
- that the photos will be used for the exercise booklet entitled ‘Individualized home-based exercise booklet’ and the thesis of Mr. Theodoros Chatzidamianos; and not for commercial reasons.
- that the photos will not reveal my facial features.
- that my anonymity is guaranteed.

I agree to be the model for the photo shoot.

 Name of Participant	 Date	 Signature
 Name of Researcher	 Date	 Signature



**Appendix 8.60. Ethical approval for the 'Step two' (RCT) granted by the HPDA.**



**ΕΠΙΚΟΥΡΟΣ**  
**Study, management and support**  
**of movement and cognition disorders**  
 non political and non profit organisation

Athens 2<sup>nd</sup> February 2015

The Scientific Committee of the non-religious, non-political, and non-profit Parkinson's Disease Association of Greece 'Epikouros kinisi' gives permission to Mr. Theodoros Chatzidamianos to conduct the exercise programme (Phase 2) of his study entitled:

"The effectiveness of a group exercise programme on improving anxiety, depression, quality of life and prevention of falls in Greek elderly population suffering from Parkinson's Disease"

as it is consistent with ethics and purposes of 'Epikouros kinisi'. The exercise programme will be performed in community areas that have been offered to 'Epikouros kinisi' by Municipalities of Athens Metropolitan Area for the free provision of services to patients with Parkinson's Disease and their caregivers. The exercise programme will be performed in five Municipalities: Elliniko-Argyroupoli, Ilioupoli, Palaio Faliro, Peristeri and Galatsi. In addition, it is allowed to provide the participants of the study with relevant exercise booklets.

The study will be conducted with cooperation and under the supervision of 'Epikouros kinisi'. 'Epikouros kinisi' is a non-religious, non-political, and non-profit organisation and a member of the European Parkinson's Disease Association (E.P.D.A.). The main aim of our organisation is the improvement of the quality of life of people living with Parkinson's disease and their families and carers; to offer new treatments for management of the disease and provide new information and guidance to Parkinson's Disease patients, their carers, society and scientific community.

On behalf of the board of 'Epikouros' and president of 'Epikouros kinisi'

Panagiotis I. Zikos



**ΕΠΙΚΟΥΡΟΣ**  
**ΑΜΚΕ ΤΡΙΑΝΤΑΦΥΛΛΙΔΗ 40**  
**ΑΘΗΝΑ ΑΦΜ. 998858340**  
**ΔΟΥ Ν. ΨΥΧΙΚΟΥ**

Epikouros tel: +30 210 2224466, www.parkinsonportal.gr, e-mail: info@parkinsonportal.gr

**Appendix 8.61.** Indications for determination of exercise (adopted from ACSM, 2014).Absolute indications

1. Suspicion of a myocardial infarction or acute myocardial infarction (heart attack)
2. Onset of moderate-to-severe angina (chest pain)
3. Drop in SBP below standing resting pressure or drop in SBP with increasing workload accompanied by signs or symptoms
4. Signs of poor perfusion (circulation or blood flow), including pallor (pale appearance to the skin), cyanosis (bluish discoloration), or cold and clammy skin
5. Severe or unusual shortness of breath
6. Central nervous system symptoms:
  - e.g., ataxia (failure of muscular coordination), vertigo (An illusion of dizzying movement), visual or gait (pattern of walking or running) problems, confusion
7. Serious arrhythmias (abnormal heart rhythms)
  - e.g.: second / third degree AV block, atrial fibrillation with fast ventricular response, increasing premature ventricular contractions or sustained ventricular tachycardia)
8. Technical inability to monitor the electrocardiogram (ECG)
9. Patient's request (to stop)

Relative indications

1. Any chest pain that is increasing
2. Physical or verbal manifestations of shortness of breath or severe fatigue
3. Wheezing
4. Leg cramps or intermittent claudication (grade 3 on a 4-point scale)
5. Hypertensive response (SBP >260 mm Hg; DBP >115 mm Hg)
6. Pronounced ECG changes from baseline
  - >2 mm of horizontal or down sloping ST- segment depression, or >2 mm of ST- segment elevation (except in aVR)
7. Exercise-induced bundle branch block that cannot be distinguished from ventricular tachycardia
8. Less serious arrhythmias (abnormal heart rhythms) such as supraventricular tachycardia

**Appendix 8.62.** Basic questions of the semi-structured interview for the pilot study.

<b>01</b>	How easy or difficult was the programme?
<b>02</b>	What did you like more?
<b>03</b>	What did you like less?
<b>04</b>	Did you experience pain or any other somatic symptoms, while doing the exercises or after the end of each session?
<b>05</b>	Where the instructions of the group-based exercise understood?
<b>06</b>	Where the instructions of the booklet and relevant images understood?
<b>07</b>	What is your opinion about the: exercise diary, walking diary, FD and FQ?
<b>08</b>	What would you like to change in the whole programme?
<b>09</b>	Anything else you would like to add?
<b>10</b>	If you have the chance, will you participate in the current study?

**Appendix 9.1.** All the co-morbidities of participants, plus previous surgical operations (for the whole sample).

Type of co-morbidities	Co-morbidities	Number of patients	Notes
Cardiovascular disease	Hypertension	21	
	Cardiac arrhythmia	3	
	Cardiac valvulopathy	3	
	Coronary artery disease	2	
	Peripheral arterial disease	1	
Respiratory disease	Bronchial asthma	1	
	COPD	1	
Musculoskeletal disease	Low back pain	23	
	Osteoarthritis	19	
	Osteoporosis	14	
	Cervical syndrome	6	
	Rheumatoid arthritis	2	
	Carpal tunnel syndrome	1	
	De Quervain syndrome	1	
	Lateral epicondylitis	1	
Neurological disease (except PD)	Stroke	2	
Other disease	Hyperlipidemia	19	
	Diabetes mellitus type 2	15	
	Hypothyroidism	6	
	Irritable bowel syndrome	4	
	Hyperthyroidism	1	
	Ulcerative colitis	1	
Most reported surgical operations	Hernia surgery	17	inguinal hernia surgery (n= 12), umbilical hernia surgery (n= 5)
	Hysterectomy	12	
	Joint replacement	8	knee replacement (n= 6), hip replacement (n= 2)
	Cancer surgery	7	breast cancer surgery (n= 5)
	Cholecystectomy	7	
	Enlarged prostate surgery	6	
	Surgery due to fracture	5	
	Pacemaker surgery	2	
	Bypass surgery	2	
	Carpal tunnel surgery	2	

Acronyms. COPD: chronic obstructive chronic disease.